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**UNITED STATES DISTRICT COURT**
**DISTRICT OF NEW JERSEY**

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| **CELGENE CORPORATION,**<br><br>**Plaintiff,**<br>**v.**<br><br>**WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED and HIKMA PHARMACEUTICALS USA, INC.,**<br><br>**Defendants.** | **Civil Action No. _____**<br><br>**COMPLAINT FOR PATENT INFRINGEMENT**<br><br>**(Filed Electronically)** |

Plaintiff Celgene Corporation ("Celgene"), by its undersigned attorneys, for its Complaint against Defendants West-Ward Pharmaceuticals International Ltd. and Hikma Pharmaceuticals USA, Inc. (collectively, "West-Ward"), alleges as follows:

## Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq*., arising from West-Ward's filing of Abbreviated New Drug Application ("ANDA") No. 211947 ("West-Ward's ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market generic versions of Celgene's 50 mg, 100 mg, 150 mg, and 200 mg THALOMID® drug products ("West-Ward's ANDA Products") prior to the expiration of United States Patent Nos. 6,315,720 (the "'720

patent"), 6,561,977 (the "'977 patent"), 6,755,784 (the "'784 patent"), 6,869,399 (the "'399 patent"), 7,141,018 (the "'018 patent"), 7,230,012 (the "'012 patent"), 7,959,566 (the "'566 patent"), 8,315,886 (the "'886 patent"), and 8,626,531 (the "'531 patent"), all owned by Celgene (collectively, "the patents-in-suit").

**The Parties**

2. Plaintiff Celgene is a biopharmaceutical company committed to improving the lives of patients worldwide. Celgene focuses on, and invests heavily in, the discovery and development of products for the treatment of severe and life-threatening conditions. Celgene is a world leader in the treatment of many such diseases, including cancer. Celgene is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 86 Morris Avenue, Summit, New Jersey 07901.

3. On information and belief, Defendant West-Ward Pharmaceuticals International Limited ("West-Ward Pharma") is a United Kingdom Corporation, having a principal place of business at 1 New Burlington Place, London, England W1S 2HR.

4. On information and belief, Defendant Hikma Pharmaceuticals USA, Inc. ("Hikma") is a Delaware corporation, having a principal place of business at 246 Industrial Way West, Eatontown, New Jersey 07724.

5. On information and belief, West-Ward Pharma and Hikma are wholly owned subsidiaries of Hikma Pharmaceuticals, PLC.

**The Patents-in-Suit**

6. On November 13, 2001, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '720 patent, entitled, "Methods for Delivering a Drug to a Patient While Avoiding the Occurrence of an Adverse Side Effect Known or Suspected of

Being Caused by the Drug," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '720 patent is attached hereto as Exhibit A.

7. On May 13, 2003, the USPTO duly and lawfully issued the '977 patent, entitled, "Methods for Delivering a Drug to a Patient While Restricting Access to the Drug by Patients for Whom the Drug May be Contraindicated," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '977 patent is attached hereto as Exhibit B.

8. On June 29, 2004, the USPTO duly and lawfully issued the '784 patent, entitled, "Methods for Delivering a Drug to a Patient While Restricting Access to the Drug by Patients for Whom the Drug May be Contraindicated," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '784 patent is attached hereto as Exhibit C.

9. On March 22, 2005, the USPTO duly and lawfully issued the '399 patent, entitled, "Methods for Delivering a Drug to a Patient While Restricting Access to the Drug by Patients for Whom the Drug May be Contraindicated," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '399 patent is attached hereto as Exhibit D.

10. On November 28, 2006, the USPTO duly and lawfully issued the '018 patent, entitled, "Methods for Delivering a Drug to a Patient While Restricting Access to the Drug by Patients for Whom the Drug May be Contraindicated," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '018 patent is attached hereto as Exhibit E.

11. On June 12, 2007, the USPTO duly and lawfully issued the '012 patent, entitled, "Pharmaceutical Compositions and Dosage Forms of Thalidomide," to Celgene as assignee of

the inventors Paul D'Angio and John McCarty. A copy of the '012 patent is attached hereto as Exhibit F.

12. On June 14, 2011, the USPTO duly and lawfully issued the '566 patent, entitled, "Methods for Delivering a Drug to a Patient While Restricting Access to the Drug by Patients for Whom the Drug May be Contraindicated," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '566 patent is attached hereto as Exhibit G.

13. On November 20, 2012, the USPTO duly and lawfully issued the '886 patent, entitled, "Methods for Delivering a Drug to a Patient While Restricting Access to the Drug by Patients for Whom the Drug May be Contraindicated," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '886 patent is attached hereto as Exhibit H.

14. On January 7, 2014, the USPTO duly and lawfully issued the '531 patent, entitled, "Methods for Delivering a Drug to a Patient While Restricting Access to the Drug by Patients for Whom the Drug May be Contraindicated," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '531 patent is attached hereto as Exhibit I.

## The THALOMID® Drug Product

15. Celgene holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for thalidomide capsules (NDA No. 20-785), which it sells under the trade name THALOMID®.

16. The claims of the patents-in-suit cover, *inter alia*, pharmaceutical compositions containing thalidomide and systems and methods of use and administration of pharmaceutical compositions containing thalidomide.

17. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the patents-in-suit are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to THALOMID®.

18. The labeling for THALOMID® instructs and encourages physicians, pharmacists, and other healthcare workers and patients to administer THALOMID® according to one or more of the methods claimed in the patents-in-suit.

**Jurisdiction and Venue**

19. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

20. The Court has personal jurisdiction over West-Ward by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

21. On information and belief, West-Ward develops, manufactures, distributes, markets, offers to sell, and sells generic drug products for sale and use throughout the United States, including within this Judicial District.

22. On information and belief, West-Ward prepares and/or aids in the submission of ANDAs to the FDA.

23. On information and belief, West-Ward derives substantial revenue from selling generic products throughout the United States, including in this Judicial District.

24. This Court has personal jurisdiction over West-Ward because, *inter alia*, it has committed an act of patent infringement under 35 U.S.C. § 271(e)(2) and has sent notice of that infringement to Celgene in the State of New Jersey. On information and belief, West-Ward intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will continue to lead to foreseeable harm and injury to Celgene in New Jersey, including in this Judicial District.

25. On information and belief, West-Ward Pharma and Hikma both actively participated in the submission of West-Ward's ANDA. On information and belief, West-Ward Pharma will work in concert with Hikma and/or other subsidiaries of Hikma Pharmaceuticals, PLC towards the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products, including West-Ward's ANDA Products, throughout the United States, including in New Jersey and in this Judicial District, prior to the expiration of the patents-in-suit.

26. On information and belief, West-Ward seeks approval from the FDA to sell West-Ward's ANDA Products throughout the United States, including in this Judicial District. On information and belief, this Judicial District will be a destination for the generic drug product described in West-Ward's ANDA.

27. This Court has personal jurisdiction over West-Ward because West-Ward has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, West-Ward regularly and continuously transacts business within New Jersey, directly or indirectly, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey. For example, West-Ward's website states "[c]urrently, we manufacture hundreds of generic medicines in the US." http://www.hikma.com/products/us-products/ (last visited August 6, 2018).

28. This Court has personal jurisdiction over West-Ward Pharma by virtue of, *inter alia*, (1) its systematic and continuous contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey, directly or indirectly, through Hikma; and (2) because it has purposefully availed itself of the privilege of

doing business in New Jersey, including directly or indirectly through its agent and/or alter ego, Hikma, a company registered with the State of New Jersey as a drug wholesaler and manufacturer. On information and belief, West-Ward Pharma purposefully has conducted and continues to conduct business in this Judicial District.

29. On information and belief, West-Ward Pharma is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District.

30. On information and belief, West-Ward Pharma, alone or through Hikma, or through distributors, retailers, and/or wholesalers, manufactures and/or distributes generic drugs for sale and use throughout the United States, including in this Judicial District.

31. On information and belief, West-Ward Pharma has previously consented to this Court's jurisdiction and has availed itself of the protections afforded by the Court by asserting counterclaims against plaintiffs in this Judicial District. *See, e.g., Forest Labs., LLC, et al. v. West-Ward Pharm. Int'l Ltd., et al.*, Civil Action No. 17-10321 (D.N.J.) (ES)(SCM).

32. In the alternative, this Court has personal jurisdiction over West-Ward Pharma because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Celgene's claims arise under federal law; (b) West-Ward Pharma is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) West-Ward Pharma has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over West-Ward Pharma satisfies due process.

33. On information and belief, Hikma is the U.S. agent for ANDA No. 211947.

34. This Court has personal jurisdiction over Hikma by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. On information and belief, Hikma purposefully has conducted and continues to conduct business in this Judicial District.

35. On information and belief, Hikma is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business ID No. 0100487525. On information and belief, Hikma is registered with the State of New Jersey's Department of Health as a wholesaler and manufacturer under Registration No. 5002130.

36. On information and belief, Hikma is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District.

37. On information and belief, Hikma, alone or through West-Ward Pharma, or through distributors, retailers, and/or wholesalers, manufactures and/or distributes generic drugs for sale and use throughout the United States, including in this Judicial District.

38. On information and belief, Hikma has a physical place of business in New Jersey.

39. On information and belief, Hikma was formerly known as West-Ward Pharmaceuticals Corp.

40. On information and belief, Hikma has previously consented to this Court's jurisdiction and has availed itself of the protections afforded by the Court by asserting counterclaims under its former name "West-Ward Pharmaceuticals Corp." against plaintiffs in this Judicial District. *See, e.g., Forest Labs., LLC, et al. v. West-Ward Pharm. Int'l Ltd., et al.,*

Civil Action No. 17-10321 (D.N.J.) (ES)(SCM); *GlaxoSmithKline PLC, et al. v. Hikma Pharmaceutical Co., Ltd., et al.*, Civil Action No. 12-1965 (D.N.J.) (FLW)(DEA).

41. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and/or 1400(b).

**Acts Giving Rise To This Suit**

42. Pursuant to Section 505 of the FFDCA, West-Ward filed West-Ward's ANDA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of West-Ward's ANDA Products, before the patents-in-suit expire.

43. On information and belief, following FDA approval of West-Ward's ANDA, West-Ward will make, use, offer to sell, or sell West-Ward's ANDA Products throughout the United States, or import such generic products into the United States.

44. On information and belief, in connection with the filing of its ANDA as described above, West-Ward provided a written certification to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("West-Ward's Paragraph IV Certification"), alleging that the claims of the patents-in-suit are invalid and/or will not be infringed by the activities described in West-Ward's ANDA.

45. No earlier than July 19, 2018, West-Ward sent written notice of West-Ward's Paragraph IV Certification to Celgene ("West-Ward's Notice Letter"). West-Ward's Notice Letter alleges that the claims of the patents-in-suit are invalid and/or will not be infringed by the activities described in West-Ward's ANDA. West-Ward's Notice Letter also informed Celgene that West-Ward seeks approval to market West-Ward's ANDA Products before the patents-in-suit expire. West-Ward specifically directed West-Ward's Notice Letter to Celgene's headquarters in Summit, New Jersey, in this Judicial District.

**Count I**
**(Infringement of the '720 Patent)**

46. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

47. West-Ward's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of West-Ward's ANDA Products, prior to the expiration of the '720 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

48. There is a justiciable controversy between the parties hereto as to the infringement of the '720 patent.

49. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will infringe one or more claims of the '720 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States.

50. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will induce infringement of one or more claims of the '720 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, upon FDA approval of West-Ward's ANDA, West-Ward will intentionally encourage acts of direct infringement with knowledge of the '720 patent and knowledge that its acts are encouraging infringement.

51. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will contributorily infringe one or more claims of the '720 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, West-Ward has had and continues to

have knowledge that West-Ward's ANDA Products are especially adapted for a use that infringes one or more claims of the '720 patent and that there is no substantial non-infringing use for West-Ward's ANDA Products.

52. Celgene will be substantially and irreparably damaged and harmed if West-Ward's infringement of the '720 patent is not enjoined.

53. Celgene does not have an adequate remedy at law.

54. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count II**
**(Infringement of the '977 Patent)**

55. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

56. West-Ward's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of West-Ward's ANDA Products, prior to the expiration of the '977 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

57. There is a justiciable controversy between the parties hereto as to the infringement of the '977 patent.

58. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will infringe one or more claims of the '977 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States.

59. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will induce infringement of one or more claims of the '977 patent under 35 U.S.C. §

271(b) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, upon FDA approval of West-Ward's ANDA, West-Ward will intentionally encourage acts of direct infringement with knowledge of the '977 patent and knowledge that its acts are encouraging infringement.

60. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will contributorily infringe one or more claims of the '977 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, West-Ward has had and continues to have knowledge that West-Ward's ANDA Products are especially adapted for a use that infringes one or more claims of the '977 patent and that there is no substantial non-infringing use for West-Ward's ANDA Products.

61. Celgene will be substantially and irreparably damaged and harmed if West-Ward's infringement of the '977 patent is not enjoined.

62. Celgene does not have an adequate remedy at law.

63. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count III**
**(Infringement of the '784 Patent)**

64. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

65. West-Ward's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of West-Ward's ANDA Products, prior to the expiration of the '784 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

66. There is a justiciable controversy between the parties hereto as to the infringement of the '784 patent.

67. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will infringe one or more claims of the '784 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States.

68. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will induce infringement of one or more claims of the '784 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, upon FDA approval of West-Ward's ANDA, West-Ward will intentionally encourage acts of direct infringement with knowledge of the '784 patent and knowledge that its acts are encouraging infringement.

69. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will contributorily infringe one or more claims of the '784 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, West-Ward has had and continues to have knowledge that West-Ward's ANDA Products are especially adapted for a use that infringes one or more claims of the '784 patent and that there is no substantial non-infringing use for West-Ward's ANDA Products.

70. Celgene will be substantially and irreparably damaged and harmed if West-Ward's infringement of the '784 patent is not enjoined.

71. Celgene does not have an adequate remedy at law.

72. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count IV**
**(Infringement of the '399 Patent)**

73. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

74. West-Ward's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of West-Ward's ANDA Products, prior to the expiration of the '399 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

75. There is a justiciable controversy between the parties hereto as to the infringement of the '399 patent.

76. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will infringe one or more claims of the '399 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States.

77. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will induce infringement of one or more claims of the '399 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, upon FDA approval of West-Ward's ANDA, West-Ward will intentionally encourage acts of direct infringement with knowledge of the '399 patent and knowledge that its acts are encouraging infringement.

78. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will contributorily infringe one or more claims of the '399 patent under 35 U.S.C. §

271(c) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, West-Ward has had and continues to have knowledge that West-Ward's ANDA Products are especially adapted for a use that infringes one or more claims of the '399 patent and that there is no substantial non-infringing use for West-Ward's ANDA Products.

79. Celgene will be substantially and irreparably damaged and harmed if West-Ward's infringement of the '399 patent is not enjoined.

80. Celgene does not have an adequate remedy at law.

81. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count V**
**(Infringement of the '018 Patent)**

82. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

83. West-Ward's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of West-Ward's ANDA Products, prior to the expiration of the '018 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

84. There is a justiciable controversy between the parties hereto as to the infringement of the '018 patent.

85. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will infringe one or more claims of the '018 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States.

86. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will induce infringement of one or more claims of the '018 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, upon FDA approval of West-Ward's ANDA, West-Ward will intentionally encourage acts of direct infringement with knowledge of the '018 patent and knowledge that its acts are encouraging infringement.

87. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will contributorily infringe one or more claims of the '018 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, West-Ward has had and continues to have knowledge that West-Ward's ANDA Products are especially adapted for a use that infringes one or more claims of the '018 patent and that there is no substantial non-infringing use for West-Ward's ANDA Products.

88. Celgene will be substantially and irreparably damaged and harmed if West-Ward's infringement of the '018 patent is not enjoined.

89. Celgene does not have an adequate remedy at law.

90. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count VI**
**(Infringement of the '012 Patent)**

91. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

92. West-Ward's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of West-Ward's ANDA Products,

prior to the expiration of the ’012 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

93. There is a justiciable controversy between the parties hereto as to the infringement of the ’012 patent.

94. Unless enjoined by this Court, upon FDA approval of West-Ward’s ANDA, West-Ward will infringe one or more claims of the ’012 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing West-Ward’s ANDA Products in the United States.

95. Unless enjoined by this Court, upon FDA approval of West-Ward’s ANDA, West-Ward will induce infringement of one or more claims of the ’012 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing West-Ward’s ANDA Products in the United States. On information and belief, upon FDA approval of West-Ward’s ANDA, West-Ward will intentionally encourage acts of direct infringement with knowledge of the ’012 patent and knowledge that its acts are encouraging infringement.

96. Unless enjoined by this Court, upon FDA approval of West-Ward’s ANDA, West-Ward will contributorily infringe one or more claims of the ’012 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing West-Ward’s ANDA Products in the United States. On information and belief, West-Ward has had and continues to have knowledge that West-Ward’s ANDA Products are especially adapted for a use that infringes one or more claims of the ’012 patent and that there is no substantial non-infringing use for West-Ward’s ANDA Products.

97. Celgene will be substantially and irreparably damaged and harmed if West-Ward’s infringement of the ’012 patent is not enjoined.

98. Celgene does not have an adequate remedy at law.

99. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count VII**
**(Infringement of the '566 Patent)**

100. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

101. West-Ward's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of West-Ward's ANDA Products, prior to the expiration of the '566 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

102. There is a justiciable controversy between the parties hereto as to the infringement of the '566 patent.

103. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will infringe one or more claims of the '566 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States.

104. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will induce infringement of one or more claims of the '566 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, upon FDA approval of West-Ward's ANDA, West-Ward will intentionally encourage acts of direct infringement with knowledge of the '566 patent and knowledge that its acts are encouraging infringement.

105. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will contributorily infringe one or more claims of the '566 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, West-Ward has had and continues to have knowledge that West-Ward's ANDA Products are especially adapted for a use that infringes one or more claims of the '566 patent and that there is no substantial non-infringing use for West-Ward's ANDA Products.

106. Celgene will be substantially and irreparably damaged and harmed if West-Ward's infringement of the '566 patent is not enjoined.

107. Celgene does not have an adequate remedy at law.

108. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count VIII**
**(Infringement of the '886 Patent)**

109. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

110. West-Ward's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of West-Ward's ANDA Products, prior to the expiration of the '886 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

111. There is a justiciable controversy between the parties hereto as to the infringement of the '886 patent.

112. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will infringe one or more claims of the '886 patent under 35 U.S.C. § 271(a) by

making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States.

113. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will induce infringement of one or more claims of the '886 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, upon FDA approval of West-Ward's ANDA, West-Ward will intentionally encourage acts of direct infringement with knowledge of the '886 patent and knowledge that its acts are encouraging infringement.

114. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will contributorily infringe one or more claims of the '886 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, West-Ward has had and continues to have knowledge that West-Ward's ANDA Products are especially adapted for a use that infringes one or more claims of the '886 patent and that there is no substantial non-infringing use for West-Ward's ANDA Products.

115. Celgene will be substantially and irreparably damaged and harmed if West-Ward's infringement of the '886 patent is not enjoined.

116. Celgene does not have an adequate remedy at law.

117. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count IX**
**(Infringement of the '531 Patent)**

118. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

119. West-Ward's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of West-Ward's ANDA Products, prior to the expiration of the '531 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

120. There is a justiciable controversy between the parties hereto as to the infringement of the '531 patent.

121. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will infringe one or more claims of the '531 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States.

122. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will induce infringement of one or more claims of the '531 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, upon FDA approval of West-Ward's ANDA, West-Ward will intentionally encourage acts of direct infringement with knowledge of the '531 patent and knowledge that its acts are encouraging infringement.

123. Unless enjoined by this Court, upon FDA approval of West-Ward's ANDA, West-Ward will contributorily infringe one or more claims of the '531 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing West-Ward's ANDA Products in the United States. On information and belief, West-Ward has had and continues to have knowledge that West-Ward's ANDA Products are especially adapted for a use that infringes one or more claims of the '531 patent and that there is no substantial non-infringing use for West-Ward's ANDA Products.

124. Celgene will be substantially and irreparably damaged and harmed if West-Ward's infringement of the '531 patent is not enjoined.

125. Celgene does not have an adequate remedy at law.

126. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**PRAYER FOR RELIEF**

WHEREFORE, Plaintiff Celgene respectfully requests the following relief:

(A) A Judgment that West-Ward has infringed the patents-in-suit by submitting ANDA No. 211947;

(B) A Judgment that West-Ward has infringed, and that West-Ward's making, using, offering to sell, selling, or importing West-Ward's ANDA Products will infringe one or more claims of the patents-in-suit;

(C) An Order that the effective date of FDA approval of ANDA No. 211947 be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which Celgene is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining West-Ward and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing West-Ward's ANDA Products until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Celgene is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining West-Ward, its officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any pharmaceutical compositions containing thalidomide or systems or methods as claimed in the patents-in-suit, or from actively inducing or contributing to

the infringement of any claim of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Celgene is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of West-Ward's ANDA Products will directly infringe, induce and/or contribute to infringement of the patents-in-suit;

(G) To the extent that West-Ward has committed any acts with respect to pharmaceutical compositions containing thalidomide or systems or methods claimed in the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Celgene damages for such acts;

(H) If West-Ward engages in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of West-Ward's ANDA Products prior to the expiration of the patents-in-suit, a Judgment awarding damages to Celgene resulting from such infringement, together with interest;

(I) A Judgment declaring that the patents-in-suit remain valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding Celgene its attorneys' fees incurred in this action;

(K) A Judgment awarding Celgene its costs and expenses incurred in this action; and

(L) Such further and other relief as this Court may deem just and proper.

Dated: August 31, 2018

By: s/ Charles M. Lizza

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**CERTIFICATION PURSUANT TO L. CIV. R. 11.2 & 40.1**

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matters captioned *Celgene Corporation v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 18-6378 (SDW)(LDW) (D.N.J.), *Celgene Corporation v. Lotus Pharm. Co., Ltd., et al.*, Civil Action No. 17-6842 (SDW)(LDW) (D.N.J.), and *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 17-3387 (ES)(MAH) (D.N.J.) are related to the matter in controversy because the matter in controversy involves the same plaintiff and some of the same patents, but Defendants are seeking FDA approval to market generic versions of different pharmaceutical products.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: August 31, 2018

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# EXHIBIT A

US006315720B1

(12) **United States Patent**
**Williams et al.**

(10) **Patent No.: US 6,315,720 B1**
(45) **Date of Patent: Nov. 13, 2001**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE AVOIDING THE OCCURRENCE OF AN ADVERSE SIDE EFFECT KNOWN OR SUSPECTED OF BEING CAUSED BY THE DRUG**

(75) Inventors: **Bruce A. Williams**, Flemington; **Joseph K. Kaminski**, Hampton, both of NJ (US)

(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/694,217**

(22) Filed: **Oct. 23, 2000**

(51) **Int. Cl.**[7] ..... **A61B 5/00**
(52) **U.S. Cl.** ..... **600/300**; 235/375
(58) **Field of Search** ..... 600/300, 304, 600/551; 395/202–210; 128/630; 706/23, 2, 3; 235/375

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(57) **ABSTRACT**

Improved methods for delivering to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug are disclosed. The methods are of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber, pharmacy and patient have been properly registered in the medium before the patient is approved to receive the drug. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to the side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

**32 Claims, No Drawings**

# METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE AVOIDING THE OCCURRENCE OF AN ADVERSE SIDE EFFECT KNOWN OR SUSPECTED OF BEING CAUSED BY THE DRUG

## FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

## BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

## SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;

b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups; and

d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.



The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for

example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or

the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is

contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional

pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuburculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be

generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the

patient is directed to return to the prescriber for detenriination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

**1**. In a method for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by said drug, wherein said method is of the type in which prescriptions for said drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in said medium and qualified to prescribe said drug, that the pharmacy is registered in said medium and qualified to fill the prescription for said drug, and the patient is registered in said medium and approved to receive said drug, the improvement comprising:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for said drug;

b. defining a set of information to be obtained from said patient, which information is probative of the risk that said adverse side effect is likely to occur if said drug is taken by said patient;

c. in response to said information set, assigning said patient to at least one of said risk groups and entering said risk group assignment in said medium;

d. based upon said information and said risk group assignment, determining whether the risk that said adverse side effect is likely to occur is acceptable; and

e. upon a determination that said risk is acceptable, generating a prescription approval code to be retrieved by said pharmacy before said prescription is filled.

**2**. The method of claim **1** wherein, in response to said risk group assignment, said patient is counseled as to the risks of taking said drug and advised as to risk avoidance measures.

**3**. The method of claim **2** wherein said counseling comprises full disclosure of said risks.

**4**. The method of claim **3** wherein said prescription is filled only following said full disclosure and informed consent of said patient.

**5**. The method of claim **4** wherein said risk group assignment and said informed consent is verified by said prescriber at the time that said patient is registered in said computer readable storage medium.

**6**. The method of claim **5** wherein said risk group assignment and said informed consent is transmitted to said computer readable storage medium by facsimile and interpreted by optical character recognition software.

**7**. The method of claim **1** wherein said set of information includes the results of diagnostic testing.

**8**. The method of claim **7** wherein said diagnostic testing is probative of the onset of said adverse side effect.

**9**. The method of claim **7** wherein said diagnostic testing is probative of the concentration of said drug in a tissue of said patient.

**10**. The method of claim **7** wherein said diagnostic testing comprises genetic testing.

11. The method of claim 1 wherein said side effect is likely to arise in said patient.

12. The method of claim 1 wherein said side effect is likely to arise in a foetus carried by said patient.

13. The method of claim 1 wherein said side effect is likely to arise in a recipient or a foetus carried by a recipient of the bodily fluid of said patient.

14. The method of claim 13 wherein said recipient is a sexual partner of said patient.

15. The method of claim 1 further comprising:

f. defining for each said risk group a second set of information to be collected from said patient on a periodic basis;

g. obtaining said second set of information from said patient; and

h. entering said second set of information in said medium before said patient is approved to receive said drug.

16. The method of claim 15 wherein said second set of information comprises a survey regarding said patient's behavior and compliance with said risk avoidance measures.

17. The method of claim 16 wherein said survey is conducted telephonically using an integrated voice response system.

18. The method of claim 16 wherein said patient is a female of childbearing potential and said second set of information comprises the results of a pregnancy test.

19. The method of claim 18 wherein said periodic interval comprises about 28 days.

20. The method of claim 1 further comprising providing said patient with a contraceptive device or formulation.

21. The method of claim 1 wherein said adverse side effect comprises a teratogenic effect.

22. The method of claim 1 wherein said drug is thalidomide.

23. The method of claim 21 wherein said teratogenic effect is likely to arise in a foetus carried by said patient.

24. The method of claim 21 wherein said teratogenic effect is likely to arise in a foetus carried by a recipient of the bodily fluid of said patient.

25. The method of claim 24 wherein said recipient of the bodily fluid of said patient is a sexual partner of said patient.

26. The method of claim 21 wherein said set of information includes the results of a pregnancy test.

27. The method of claim 26 wherein said prescription is filled for no more than about 28 days.

28. In a method for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by said drug, wherein said method is of the type in which prescriptions for said drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in said medium and qualified to prescribe said drug, that the pharmacy is registered in said medium and qualified to fill the prescription for said drug, and the patient is registered in said medium and approved to receive said drug, the improvement comprising:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for said drug;

b. defining a set of information to be obtained from said patient, which information is probative of the risk that said adverse side effect is likely to occur if said drug is taken by said patient;

c. in response to said information set, assigning said patient to at least one of said risk groups and entering said risk group assignment in said medium;

d. based upon said information and said risk group assignment, determining whether the risk that said adverse side effect is likely to occur is acceptable; and

e. upon a determination that said risk is acceptable, generating a prescription approval code to be retrieved by said pharmacy before said prescription is filled,

wherein said adverse side effect is likely to arise in patients who take said drug in combination with at least one other drug.

29. The method of claim 28 wherein said set of information is also probative of the likelihood that said patient may take said drug and said other drug in combination.

30. The method of claim 28 wherein said set of information includes the results of diagnostic testing.

31. The method of claim 30 wherein said diagnostic testing comprises testing for evidence of the use of said other drug.

32. The method of claim 30 wherein said diagnostic testing comprises testing for evidence which is indicative of the onset of said adverse side effect.

* * * * *

# EXHIBIT B

US006561977B2

(12) **United States Patent**
**Williams et al.**

(10) **Patent No.: US 6,561,977 B2**
(45) **Date of Patent: *May 13, 2003**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/965,155**

(22) Filed: **Sep. 27, 2001**

(65) **Prior Publication Data**

US 2002/0052543 A1 May 2, 2002

**Related U.S. Application Data**

(63) Continuation of application No. 09/694,217, filed on Oct. 23, 2000, now Pat. No. 6,315,720.

(51) **Int. Cl.**[7] ..... **A61B 5/00**; G06F 17/00

(52) **U.S. Cl.** ..... **600/300**; 128/920; 235/375; 705/3; 702/19

(58) **Field of Search** ..... 600/300–301, 600/304, 551; 395/202–210; 706/23, 2–3; 705/2–4; 735/375; 707/102

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

**34 Claims, No Drawings**

# METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

## CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. application Ser. No. 09/694,217, filed Oct. 23, 2000 U.S. Pat. No. 6,315,720.

## FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

## BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.



In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

## SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;

b. defining a set of information to be obtained from the patient, which information is probative of the risk that

such adverse side effect is likely to occur if the drug is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups; and

d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registra-

tion card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the

drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided

verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will

be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing.

Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuburculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescript2ion to a registered pharmacy, the computer readable storage medium is consulted to verify tha2t the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for

the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence

amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed is:

**1**. A method for delivering a drug to patients in need of the drug while restricting access to the drug by patients for whom the drug may be contraindicated, said method comprising permitting prescriptions for the drug to be filled by a pharmacy only after the pharmacy has retrieved an approval code for the prescription from a computer readable storage medium, wherein generation of the prescription approval code comprises the following steps:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;

b. defining a set of information to be obtained from a patient, which information is probative of the risk that an adverse side effect is likely to occur if the drug is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups and entering the patient, the information and the patient's risk group assignment in the medium;

d. based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and

e. upon a determination that the risk is acceptable, generating the prescription approval code to be retrieved by the pharmacy before the prescription is filled.

**2**. A method according to claim **1** further comprising registering in the medium the physician who prescribed the drug.

**3**. A method according to claim **1** further comprising registering the pharmacy in the medium.

**4**. The method of claim **1** further comprising counseling the patient as to the risks of taking the drug and advising the patient as to risk avoidance measures, in response to the risk group assignment.

**5**. The method of claim **4** wherein the counseling comprises full disclosure of the risks.

**6**. The method of claim **5** wherein the prescription is filled only following the full disclosure and informed consent of the patient.

**7**. The method of claim **6** wherein the informed consent is registered in the computer readable storage medium prior to generation of the prescription approval code.

**8**. The method of claim **7** wherein the risk group assignment and the informed consent is transmitted to the computer readable storage medium by facsimile and interpreted by optical character recognition software.

**9**. The method of claim **1** wherein the set of information includes the results of diagnostic testing.

**10**. The method of claim **9** wherein the diagnostic testing comprises genetic testing.

**11**. The method of claim **9** wherein the diagnostic testing is probative of the onset of the adverse side effect.

**12**. The method of claim **9** wherein the diagnostic testing is probative of the presence of a condition or disease for which the drug is contraindicated.

**13**. The method of claim **1** wherein the side effect is likely to arise in the patient.

**14**. The method of claim **1** wherein the side effect is likely to arise in a foetus carried by the patient.

**15**. The method of claim **1** wherein the side effect is likely to arise in a recipient or a foetus carried by a recipient of the bodily fluid of the patient.

**16**. The method of claim **15** wherein the recipient is a sexual partner of the patient.

**17**. The method of claim **1** further comprising:

f. defining for each risk group a second set of information to be collected from the patient at periodic intervals;

g. obtaining the second set of information from the patient; and

h. entering the second set of information in the medium.

**18**. The method of claim **17** wherein the second set of information comprises a survey regarding the patient's behavior and compliance with the risk avoidance measures.

**19**. The method of claim **18** wherein the survey is conducted telephonically using an integrated voice response system.

**20**. The method of claim **17** wherein the patient is a female of childbearing potential and the second set of information comprises the results of a pregnancy test.

**21**. The method of claim **18** wherein the periodic interval comprises about 28 days.

**22**. The method of claim **1** further comprising providing the patient with a contraceptive device or formulation.

**23**. The method of claim **1** wherein the adverse side effect comprises a teratogenic effect.

**24**. The method of claim **23** wherein the drug is thalidomide.

**25**. The method of claim **23** wherein the teratogenic effect is likely to arise in a foetus carried by the patient.

**26**. The method of claim **23** wherein the teratogenic effect is likely to arise in a foetus carried by a recipient of the bodily fluid of the patient.

**27**. The method of claim **26** wherein the recipient of the bodily fluid of the patient is a sexual partner of the patient.

**28**. The method of claim **23** wherein the set of information includes the results of a pregnancy test.

**29**. The method of claim **28** wherein the prescription is filled for no more than about 28 days.

**30**. The method of claim **1** wherein the adverse side effect is likely to arise in patients who take the drug in combination with at least one other drug.

**31**. The method of claim **30** wherein the set of information is also probative of the likelihood that the patient may take the drug and the other drug in combination.

**32**. The method of claim **30** wherein the set of information includes the results of diagnostic testing.

**33**. The method of claim **32** wherein the diagnostic testing comprises testing for evidence of the use of the other drug.

**34**. The method of claim **32** wherein the diagnostic testing comprises testing for evidence which is indicative of the onset of the adverse side effect.

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# EXHIBIT C

US006755784B2

(12) **United States Patent**
**Williams et al.**

(10) **Patent No.: US 6,755,784 B2**
(45) **Date of Patent: *Jun. 29, 2004**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 34 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/383,275**

(22) Filed: **Mar. 7, 2003**

(65) **Prior Publication Data**

US 2003/0149345 A1 Aug. 7, 2003

**Related U.S. Application Data**

(63) Continuation of application No. 09/965,155, filed on Sep. 27, 2001, now Pat. No. 6,561,977, which is a continuation of application No. 09/694,217, filed on Oct. 23, 2000, now Pat. No. 6,315,720.

(51) **Int. Cl.**[7] ..... **A61B 5/00**
(52) **U.S. Cl.** ..... **600/300**; 128/920
(58) **Field of Search** ..... 600/301, 300, 600/304; 395/200–210; 128/920, 925, 904, 897; 707/102; 706/23; 705/2–4; 235/375

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

**34 Claims, No Drawings**

# METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

## CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of patent application Ser. No. 09/965,155, filed Sep. 27, 2001, now U.S. Pat. No. 6,561,977, which is a continuation of patent application Ser. No. 09/694,217, filed Oct. 23, 2000, now U.S. Pat. No. 6,315,720, the entirety of each of which is incorporated herein by reference.

## FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

## BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community



anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

## SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to

receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;

b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups; and

d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a

registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise

female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the

patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug.

Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuburculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the sane, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

**1**. A method for delivering a drug to patients in need of the drug while restricting access to the drug by patients for whom the drug may be contraindicated, said method comprising permitting prescriptions for the drug to be filled by a pharmacy only after the pharmacy has received an approval code for the prescription from a computer readable storage medium, wherein generation of the prescription approval code comprises the following steps:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;

b. defining a set of information to be obtained from the patient, which information is probative of the risk that an adverse side effect is likely to occur if the drug is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups and entering the patient, the information and the patient's risk group assignment into the medium;

d. based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and

e. upon a determination that the risk is acceptable, generating the prescription approval code to be received by the pharmacy before the prescription is filled.

**2**. A method according to claim **1** further comprising registering in the medium the physician who prescribed the drug.

**3**. A method according to claim **1** further comprising registering the pharmacy in the medium.

**4**. The method of claim **1** further comprising counseling the patient as to the risks of taking the drug and advising the patient as to risk avoidance measures, in response to the risk group assignment.

**5**. The method of claim **4** wherein the counseling comprises full disclosure of the risks.

**6**. The method of claim **5** wherein the prescription is filled only following the full disclosure and informed consent of the patient.

**7**. The method of claim **6** wherein the informed consent is registered in the computer readable storage medium prior to generation of the prescription approval code.

**8**. The method of claim **7** wherein the risk group assignment and the informed consent is transmitted to the com-

puter readable storage medium by facsimile and interpreted by optical character recognition software.

**9**. The method of claim **1** wherein the set of information comprises the results of diagnostic testing.

**10**. The method of claim **9** wherein the diagnostic testing comprises genetic testing.

**11**. The method of claim **9** wherein the diagnostic testing is probative of the onset of the adverse side effect.

**12**. The method of claim **9** wherein the diagnostic testing is probative of the presence of a condition or disease for which the drug is contraindicated.

**13**. The method of claim **1** wherein the side effect is likely to arise in the patient.

**14**. The method of claim **1** wherein the side effect is likely to arise in a foetus carried by the patient.

**15**. The method of claim **1** wherein the side effect is likely to arise in a recipient or a foetus carried by a recipient of the bodily fluid of the patient.

**16**. The method of claim **15** wherein the recipient is a sexual partner of the patient.

**17**. The method of claim **1** further comprising:

f. defining for each risk group a second set of information to be collected from the patient at periodic intervals;

g. obtaining the second set of information from the patient; and

h. entering the second set of information in the medium.

**18**. The method of claim **17** wherein the second set of information comprises a survey regarding the patient's behavior and compliance with the risk avoidance measures.

**19**. The method of claim **18** wherein the survey is conducted telephonically using an integrated voice response system.

**20**. The method of claim **17** herein the patient is a female of childbearing potential and the second set of information comprises the results of a pregnancy test.

**21**. The method of claim **18** wherein the periodic interval comprises about 28 days.

**22**. The method of claim **1** further comprising providing the patient with a contraceptive device or formulation.

**23**. The method of claim **1** wherein the adverse side effect comprises a teratogenic effect.

**24**. The method of claim **23** wherein the drug is thalidomide.

**25**. The method of claim **23** wherein the teratogenic effect is likely to arise in a foetus carried by the patient.

**26**. The method of claim **23** wherein the teratogenic effect is likely to arise in a foetus carried by a recipient of the bodily fluid of the patient.

**27**. The method of claim **26** wherein the recipient of the bodily fluid of the patient is a sexual partner of the patient.

**28**. The method of claim **26** wherein the set of information includes the results of a pregnancy test.

**29**. The method of claim **28** wherein the prescription is filled for more than about 28 days.

**30**. The method of claim **1** wherein the adverse side effect is likely to arise in patients who take the drug in combination with at least one other drug.

**31**. The method of claim **30** wherein the set of information is also probative of the likelihood that the patient may take the drug and the other drug in combination.

**32**. The method of claim **30** wherein the set of information includes the results of diagnostic testing.

**33**. The method of claim **32** wherein the diagnostic testing comprises testing for evidence of the use of the other drug.

**34**. The method of claim **32** wherein the diagnostic testing comprises testing for evidence which is indicative of the onset of the adverse side effect.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 6,755,784 B2
DATED : June 29, 2004
INVENTOR(S) : Bruce A. Williams and Joseph A. Kaminski

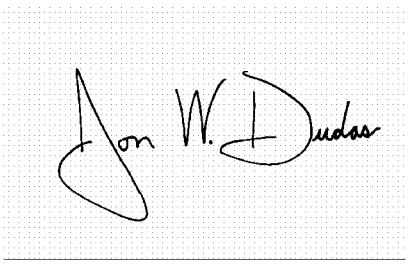


It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 20,
Line 20, cancel the text "filled for more than about 28 days." and insert -- filled for no more than about 28 days. --.

Signed and Sealed this

Third Day of May, 2005



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# EXHIBIT D

US006869399B2

(12) **United States Patent**
**Williams et al.**

(10) **Patent No.: US 6,869,399 B2**
(45) **Date of Patent: *Mar. 22, 2005**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/762,880**

(22) Filed: **Jan. 22, 2004**

(65) **Prior Publication Data**

US 2004/0152959 A1 Aug. 5, 2004

**Related U.S. Application Data**

(63) Continuation of application No. 10/383,275, filed on Mar. 7, 2003, now Pat. No. 6,755,784, which is a continuation of application No. 09/965,155, filed on Sep. 27, 2001, now Pat. No. 6,561,977, which is a continuation of application No. 09/694,217, filed on Oct. 23, 2000, now Pat. No. 6,315,720.

(51) **Int. Cl.**[7] ..... **A61B 5/00**
(52) **U.S. Cl.** ..... **600/300**; 128/920
(58) **Field of Search** ..... 600/300–301, 600/304; 702/19; 128/920; 283/900; 705/2–4

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

**19 Claims, No Drawings**

# METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is continuation of U.S. application Ser. No. 10/383,275, filed Mar. 7, 2003 now U.S. Pat. No. 6,755,784, which is a continuation of U.S. application Ser. No. 09/965,155, filed Sep. 27, 2001, now U.S. Pat. No. 6,561,977, which is a continuation of U.S. application Ser. No. 09/694,217, filed Oct. 23, 2000, now U.S. Pat. No. 6,315,720, the entirety of each of which is incorporated herein by reference.

## FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

## BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs); may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the



assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more-than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

## SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the

medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;

b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups; and

d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

## DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may

be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed

to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on

the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo

pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription,

the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuberculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system,

and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease.

Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

**1**. A method for treating erythema nodosum leprosum using thalidomide while restricting access to thalidomide for patients for whom thalidomide may be contraindicated, said method comprising permitting prescriptions for thalidomide to be filled by a pharmacy only after the pharmacy has received an approval code for the prescription from a computer readable storage medium, wherein generation of the prescription approval code comprises the following steps:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for thalidomide;

b. defining a set of information to be obtained from the patient, which information is probative of the risk that an adverse side effect is likely to occur if thalidomide is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups and entering the patient, the information and the patient's risk group assignment into the medium;

d. based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and

e. upon a determination that the risk is acceptable, generating the prescription approval code to be received by the pharmacy before the prescription is filled.

**2**. A method according to claim **1** further comprising registering in the medium the physician who prescribed the drug.

**3**. A method according to claim **1** further comprising registering the pharmacy in the medium.

**4**. The method of claim **1** further comprising counseling the patient as to the risks of taking the drug and advising the patient as to risk avoidance measures, in response to the risk group assignment.

**5**. The method of claim **4** wherein the counseling comprises full disclosure of the risks.

**6**. The method of claim **5** wherein the prescription is filled only following the full disclosure and informed consent of the patient.

7. The method of claim 6 wherein the informed consent is registered in the computer readable storage medium prior to generation of the prescription approval code.

8. The method of claim 7 wherein the risk group assignment and the informed consent is transmitted to the computer readable storage medium by facsimile and interpreted by optical character recognition software.

9. The method of claim 1 further comprising:

f. defining for each risk group a second set of information to be collected from the patient at periodic intervals;

g. obtaining the second set of information from the patient; and

h. entering the second set of information in the medium.

10. A method for treating a patient having a disease or condition which is responsive to thalidomide while restricting access to thalidomide for patients for whom thalidomide may be contraindicated, the method comprising permitting prescriptions for thalidomide to be filled by a pharmacy only after the pharmacy has become aware of approval of a prescription for thalidomide for the patient from a computer readable storage medium, the generation of the prescription approval comprising the following steps:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for thalidomide;

b. defining a set of information to be obtained from the patient, which information is probative of the risk that an adverse side effect is likely to occur if thalidomide is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups and entering the patient, the information and the patient's risk group assignment into the medium;

d. based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and

e. upon a determination that the risk is acceptable, generating the prescription approval before the prescription is filled.

11. A method according to claim 10 further comprising registering in the medium the physician who prescribed the drug.

12. A method according to claim 10 further comprising registering the pharmacy in the medium.

13. The method of claim 10 further comprising counseling the patient as to the risks of taking the drug and advising the patient as to risk avoidance measures, in response to the risk group assignment.

14. The method of claim 13 wherein the counseling comprises full disclosure of the risks.

15. The method of claim 14 wherein the prescription is filled only following the full disclosure and informed consent of the patient.

16. The method of claim 15 wherein the informed consent is registered in the computer readable storage medium prior to generation of the prescription approval.

17. The method of claim 16 wherein the risk group assignment and the informed consent is transmitted to the computer readable storage medium by facsimile and interpreted by optical character recognition software.

18. The method of claim 10 further comprising:

f. defining for each risk group a second set of information to be collected from the patient at periodic intervals;

g. obtaining the second set of information from the patient; and

h. entering the second set of information in the medium.

19. A method for treating a disease with a drug known or suspected of having teratogenic properties while restricting access to the drug by patients for whom the drug may be contraindicated the method comprising permitting prescriptions for thalidomide to be filled by a pharmacy only after the pharmacy has become aware of approval of a prescription for thalidomide for the patient from a computer readable storage medium, the generation of the prescription approval comprising the following steps:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for thalidomide;

b. defining a set of information to be obtained from the patient, which information is probative of the risk that an adverse side effect is likely to occur if thalidomide is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups and entering the patient, the information and the patient's risk group assignment into the medium;

d. based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and

e. upon a determination that the risk is acceptable, generating the prescription approval before the prescription is filled.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 6,869,399 B2
DATED : March 22, 2005
INVENTOR(S) : Williams et al.

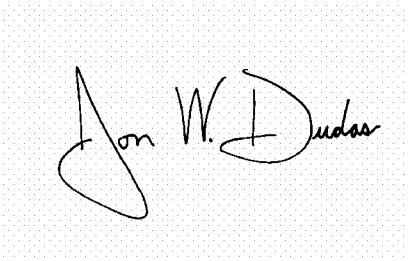


It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 20,
Lines 25, 27, 31 and 34, delete "thalidomide" and insert -- said drug --.

Signed and Sealed this

Seventh Day of March, 2006



JON W. DUDAS
*Director of the United States Patent and Trademark Office*

# EXHIBIT E

US007141018B2

(12) **United States Patent**
**Williams et al.**

(10) **Patent No.: US 7,141,018 B2**
(45) **Date of Patent: *Nov. 28, 2006**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/028,144**

(22) Filed: **Jan. 3, 2005**

(65) **Prior Publication Data**

US 2005/0176768 A1 Aug. 11, 2005

**Related U.S. Application Data**

(63) Continuation of application No. 10/762,880, filed on Jan. 22, 2004, now Pat. No. 6,869,399, which is a continuation of application No. 10/383,275, filed on Mar. 7, 2003, now Pat. No. 6,755,784, which is a continuation of application No. 09/965,155, filed on Sep. 27, 2001, now Pat. No. 6,561,977, which is a continuation of application No. 09/694,217, filed on Oct. 23, 2000, now Pat. No. 6,315,720.

(51) **Int. Cl.**
***A61B 5/00*** (2006.01)

(52) **U.S. Cl.** ..... **600/300**; 128/920; 705/2

(58) **Field of Classification Search** ..... 600/300–301; 128/898, 920; 702/19; 283/900; 705/2–4
See application file for complete search history.

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

**9 Claims, No Drawings**

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# METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 10/762,880, filed Jan. 22, 2004 now U.S. Pat. No. 6,869,399, which is a continuation of U.S. application Ser. No. 10/383,275, filed Mar. 7. 2003, now U.S. Pat. No. 6,755,784, which is a continuation of U.S. application Ser. No. 09/965,155, filed Sep. 27. 2001, now U.S. Pat. No. 6,561,977, which is a continuation of U.S. application Ser. No. 09/694,217, filed Oct. 23, 2000, now U.S. Pat. No. 6,315,720, the entirety of each of which is hereby incorporated by reference.

## FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

## BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication (s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other



diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

## SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which

prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;
c. in response to the information set, assigning the patient to at least one of the risk groups; and
d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

## DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including,

for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending

upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to

that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be

occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female

patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuburculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid,

may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other

HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

**1**. A method for treating a patient having a disease or condition which is responsive to thalidomide while restricting access to thalidomide for patients for whom thalidomide may be contraindicated, the method comprising permitting prescriptions for thalidomide to be filled by a pharmacy only after the pharmacy has become aware of the generation of a prescription approval code for thalidomide for the patient from a computer readable storage medium, the generation of said prescription approval code comprising the following steps:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for thalidomide;

b. defining a set of information to be obtained from the patient, said set of information comprising the result of a determination of the ability of the patient to become pregnant and optionally comprising a determination that the patient is either (1) not currently pregnant or (2) currently pregnant;

c. in response to said information set, assigning the patient to at least one of said risk groups and entering the patient, the information and the patient's risk group assignment into the medium;

d. based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and

e. upon a determination that the risk is acceptable, generating the prescription approval code before the prescription is filled.

**2**. A method according to claim **1** further comprising registering in the medium the physician who prescribed said thalidomide.

**3**. A method according to claim **1** further comprising registering the pharmacy in the medium.

**4**. The method of claim **1** further comprising counseling the patient as to the risks of taking the drug and advising the patient as to risk avoidance measures, in response to the risk group assignment.

5. The method of claim 4 wherein the counseling comprises full disclosure of the risks.

6. The method of claim 5 wherein the prescription is filled only following said full disclosure.

7. The method of claim 6 wherein the fact of said full disclosure is registered in the computer readable storage medium prior to generation of the prescription approval code.

8. The method of claim 7 wherein the risk group assignment and the fact of said full disclosure is transmitted to the computer readable storage medium by facsimile and interpreted by optical character recognition software.

9. The method of claim 1 further comprising:

f. defining for each risk group a second set of information to be collected from the patient at periodic intervals;

g. obtaining the second set of information from the patient; and

h. entering the second set of information in the medium.

* * * * *

# EXHIBIT F

US007230012B2

(12) **United States Patent**
**D'Angio et al.**

(10) **Patent No.: US 7,230,012 B2**
(45) **Date of Patent: Jun. 12, 2007**

(54) **PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS OF THALIDOMIDE**

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( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 162 days.

(21) Appl. No.: **10/608,077**

(22) Filed: **Jun. 30, 2003**

(65) **Prior Publication Data**

US 2004/0138263 A1 Jul. 15, 2004

**Related U.S. Application Data**

(60) Provisional application No. 60/426,016, filed on Nov. 14, 2002.

(51) **Int. Cl.**
***A61K 31/445*** (2006.01)
***A61K 9/48*** (2006.01)

(52) **U.S. Cl.** ..... **514/323**; 514/323; 424/451

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Pharmaceutical compositions and single unit dosage forms of thalidomide and pharmaceutically acceptable prodrugs, salts, solvates, hydrates, or clathrates are disclosed. Also disclosed are methods of treating and preventing diseases and conditions such as, but not limited to, leprosy, chronic graft-vs-host disease, rheumatoid arthritis, sarcoidosis, an inflammatory condition, inflammatory bowel disease, and cancer using the novel dosage forms disclosed herein.

**10 Claims, No Drawings**

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# PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS OF THALIDOMIDE

This application claims priority to provisional application No. 60/426,016, filed Nov. 14, 2002, the entirety of which is incorporated herein by reference.

## 1. FIELD OF THE INVENTION

The present invention relates, in part, to pharmaceutical compositions and dosage forms comprising thalidomide and pharmaceutically acceptable prodrugs, salts, solvates, hydrates, and clathrates thereof.

## 2. BACKGROUND OF THE INVENTION

Thalidomide is a racemic compound sold under the tradename THALOMID® and chemically named α-(N-phthalimido)glutarimide or 2-(2,6-dioxo-3-piperidinyl)-1H-isoindole-1,3(2H)-dione. Thalidomide was originally developed to treat morning sickness, but due to tetragenic effects it was withdrawn from use. Thalidomide is currently approved in the United States for the treatment of erythema nodosum leprosum in humans. *Physician's Desk Reference®,* 1081-1085 (55th ed., 2001).

Thalidomide has reportedly been used on patients with leprosy, chronic graft-vs-host disease, rheumatoid arthritis, sarcoidosis, several inflammatory skin diseases, and inflammatory bowel disease. See generally, Koch, H. P., 22 *Prog. Med. Chem.* 165-242 (1985). See also, Moller, D. R., et al., 159 *J. Immunol.* 5157-5161 (1997); Vasiliauskas, E. A., et al., 117 *Gastroenterology* 1278-1287 (1999); and Ehrenpreis, E. D., et al., 117 *Gastroenterology* 1271-1277 (1999). It has further been alleged that thalidomide can be combined with other drugs to treat iscehemia/reperfusion associated with coronary and cerebral occlusion. U.S. Pat. No. 5,643,915.

More recently, thalidomide has been used in the treatment of specific types of cancers. These include refractory multiple myeloma, brain, melanoma, breast, colon, mesothelioma, and renal cell carcinoma. See, e.g., Singhal, S., et al., 341(21) *New England J. Med.,* 1565-1571 (1999); and Marx, G. M., et al., 18 *Proc. Am. Soc. Clin. Oncology,* 454a (1999). It has further been reported that thalidomide has been used to prevent the development of chronic cardiomyopathy in rats caused by doxorubicin. Costa, P. T., et al., 92(10:suppl. 1) *Blood,* 235b (1998). Other reports concerning the use of thalidomide in the treatment of specific cancers include combination with carboplatin in the treatment of glioblastoma multiforme. McCann, J., *Drug Topics* 41-42 (Jun. 21, 1999). Thalidomide has reportedly also been used as an antiemetic during the treatment of astrocytoma. Zwart, D., 16(12) *Arzneim.-Forsch.,* 1688-1689 (1966). A method of inhibiting of angiogenesis is disclosed by U.S. Pat. No. 6,235,756 B1, which is incorporated herein by reference.

Thalidomide is administered to patients orally. Presently, thalidomide is orally administered in a size #0 capsule shell containing 12.5 percent weight by total weight of the composition. The capsule fill weight is 400 mg, so only 50 mg of thalidomide are included per capsule. For use in the treatment of diseases such as cancer, however, 200 mg to 800 mg dosages are commonly required. Therefore, patients may have to ingest 4 to 16 capsules of thalidomide to receive a therapeutically effective amount of the drug. Because of the large size of the #0 capsule and the large amount of thalidomide required to treat certain diseases and conditions, patient compliance may be problematic. To be specific, some patients may not take thalidomide in its currently available oral dosage form as often or in the large amounts necessary to effectively treat their disease. Therefore, a need exists for new pharmaceutical dosage forms of thalidomide.



## 3. SUMMARY OF THE INVENTION

This invention encompasses novel pharmaceutical dosage forms of thalidomide and pharmaceutically acceptable prodrugs, salts, solvates, hydrates, and clathrates thereof. The invention further encompasses methods of treating or preventing diseases and conditions such as, but not limited to, leprosy, chronic graft-vs-host disease, rheumatoid arthritis, sarcoidosis, an inflammatory condition, inflammatory bowel disease, and cancer, using thalidomide and pharmaceutically acceptable prodrugs, salts, solvates, hydrates, and clathrates thereof in the novel dosage forms described herein.

### 3.1. Definitions

As used herein and unless otherwise indicated, a composition that is "substantially free" of a compound means that the composition contains less than about 20 percent by weight, more preferably less than about 10 percent by weight, even more preferably less than about 5 percent by weight, and most preferably less than about 3 percent by weight of the compound.

As used herein and unless otherwise indicated, the term "stereomerically pure" means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80 percent by weight of one stereoisomer of the compound and less than about 20 percent by weight of other stereoisomers of the compound, more preferably greater than about 90 percent by weight of one stereoisomer of the compound and less than about 10 percent by weight of the other stereoisomers of the compound, even more preferably greater than about 95 percent by weight of one stereoisomer of the compound and less than about 5 percent by weight of the other stereoisomers of the compound, and most preferably greater than about 97 percent by weight of one stereoisomer of the compound and less than about 3 percent by weight of the other stereoisomers of the compound.

As used herein and unless otherwise indicated, the term "enantiomerically pure" means a stereomerically pure composition of a compound having one chiral center.

As used herein, unless otherwise specified, the term "pharmaceutically acceptable salt(s)," as used herein includes, but is not limited to, salts of acidic or basic moieties of thalidomide. Basic moieties are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that can be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions. Suitable organic acids include, but are not limited to, maleic, fumaric, benzoic, ascorbic, succinic, acetic, formic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, oleic, tannic, aspartic, stearic, palmitic, glycolic, glutamic, gluconic, glucaronic, saccharic, isonico-

tinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, benzenesulfonic acids, or pamoic (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate) acids. Suitable inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, or nitric acids. Compounds that include an amine moiety can form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Chemical moieties that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts are alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, or iron salts.

As used herein to describe a compound or chemical moiety, the term "derivative" means a compound or chemical moiety wherein the degree of saturation of at least one bond has been changed (e.g., a single bond has been changed to a double or triple bond) or wherein at least one hydrogen atom is replaced with a different atom or a chemical moiety. Examples of different atoms and chemical moieties include, but are not limited to, halogen, oxygen, nitrogen, sulfur, hydroxy, methoxy, alkyl, amine, amide, ketone, and aldehyde.

As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide the compound. Examples of prodrugs include, but are not limited to, derivatives of thalidomide that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of thalidomide that include —NO, —$NO_2$, —ONO, or —$ONO_2$ moieties.

As used herein and unless otherwise indicated, the terms "biohydrolyzable carbamate," "biohydrolyzable carbonate," "biohydrolyzable ureide," "biohydrolyzable phosphate" mean a carbamate, carbonate, ureide, or phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, aminoacids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

As used herein and unless otherwise indicated, the term "biohydrolyzable ester" means an ester of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters.

As used herein and unless otherwise indicated, the term "biohydrolyzable amide" means an amide of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound. Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α-amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides.

## 4. DETAILED DESCRIPTION OF THE INVENTION

This invention encompasses novel pharmaceutical dosage forms of thalidomide and pharmaceutically acceptable prodrugs, salts, solvates, hydrates, and clathrates thereof. Preferred dosage forms are suitable for oral administration to a patient. Preferred oral dosage forms of thalidomide comprise a higher weight percent of thalidomide than prior oral dosage forms of the drug. Preferred oral dosage forms of thalidomide are either bioequivalent to the oral dosage forms of the drug currently approved by the Food and Drug Administration in the United States, or provide better bioavailability than currently approved dosage forms.

The invention also encompasses kits comprising pharmaceutical compositions and dosage forms of the invention. Also encompassed by the invention are methods of treating and preventing diseases and conditions which include administering to patients in need thereof pharmaceutical compositions and dosage forms of the invention.

For example, this invention encompasses a single unit dosage form suitable for oral administration to a human comprising: greater than about 1, 5, 10, 15, 20, 25 mg, or 30 mg of an active ingredient; and an excipient; wherein the active ingredient is thalidomide or a pharmaceutically acceptable produg, salt, solvate, or clathrate thereof. Preferably, the amount of active ingredient is from about 5 to about 10 weight percent when the active ingredient is about 1 to about 5 mgs.

A particular embodiment of the invention encompasses a single unit dosage form suitable for oral administration to a human comprising: greater than about 25 mg of an active ingredient; and an excipient; wherein the active ingredient is thalidomide or a pharmaceutically acceptable produg, salt, solvate, or clathrate thereof. Preferably, the amount of active ingredient is from about 30 to about 50 weight percent, more preferably about 40 weight percent when the active ingredient is about 25 mgs or more.

A specific example of this embodiment is a single unit dosage form suitable for oral administration to a human comprising: about 50 mg of an active ingredient, wherein the active ingredient is thalidomide or a pharmaceutically acceptable prodrug, salt, solvate, or clathrate thereof; about 74 mg of a carrier, diluent or filler, wherein the carrier, diluent or filler comprises pregelatinized corn starch or microcrystalline cellulose or silicified microcrystalline cellulose or dicalcium phosphate; and about 1 mg of magnesium stearate; wherein the single unit dosage form is a capsule of size #4.

Another specific example encompasses a single unit dosage form suitable for oral administration to a human comprising: about 40 weight percent of an active ingredient, wherein the active ingredient is thalidomide or a pharmaceutically acceptable produg, salt, solvate, or clathrate thereof; about 53 weight percent of a binder, wherein the binder comprises pregelatinized corn starch or microcrystalline cellulose; about 4 weight percent surfactant; about 2 weight percent disintegrant; and about 1 weight percent lubricant; wherein the single unit dosage form is a tablet.

Another embodiment of the invention encompasses a method for treating or preventing leprosy, chronic graft-vs-host disease, rheumatoid arthritis, sarcoidosis, an inflammatory condition, inflammatory bowel disease, or cancer, which comprises administering to a patient in need of such

treatment or prevention a single unit dosage form of the invention. In a preferred method, the disease is cancer.

This invention encompasses pharmaceutical compositions and single unit dosage forms of racemic and stereomerically pure thalidomide, and pharmaceutically acceptable prodrugs, salts, solvates, hydrates, and clathrates thereof.

Thalidomide is commercially available, but can also be prepared by methods known in the art. See, e.g., *The Merck Index*, p. 9182 (11$^{th}$ ed.; 1989), and the references disclosed therein.

### 4.1. Pharmaceutical Compositions and Dosage Forms

Pharmaceutical compositions and dosage forms of the invention contain a prophylactically or therapeutically effective amount of an active ingredient (i.e., thalidomide or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof) and an excipient. Preferred dosage forms are suitable for oral administration, and can be coated to reduce or avoid degradation of the active ingredient within the gastrointestinal tract.

Pharmaceutical compositions and dosage forms of the invention may also contain one or more secondary active ingredients. Examples of secondary active ingredients include, but are not limited to, anti-cancer drugs. Examples of anti-cancer drugs include, but are not limited to: acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflomithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-I a; interferon gamma-I b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride. Other anti-cancer drugs include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflomithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon

agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

Preferred pharmaceutical compositions and dosage forms contain greater than about 25 weight percent active ingredient (i.e., thalidomide or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof). Pharmaceutical compositions and dosage forms are encompassed by the invention that contain the active ingredient in an amount of from about 30 percent to about 50 percent by weight, preferably from about 35 percent to about 45 percent by weight, and most preferably about 40 percent by weight of the total composition or dosage form.

Pharmaceutical compositions and dosage forms of the invention preferably contain one or more excipients in an amount of less than about 75 percent by weight of the total composition or dosage form. Pharmaceutical compositions and dosage forms are encompassed by the invention that contain the excipient(s) in an amount of from about 50 percent to about 70 percent by weight, preferably from about 55 percent to about 65 percent by weight, more preferably in an amount of about 60 percent by weight.

Excipients include carriers, diluents, fillers, lubricants and glidants. One embodiment of the invention encompasses a pharmaceutical composition that includes thalidomide, and a carrier, diluent or filler. The carrier, diluent or filler is preferably present in an amount from about 50 percent to about 75 percent by weight, preferably from about 55 percent to about 65 percent by weight. A preferred pharmaceutical composition further includes a lubricant or glidant in an amount of from about 0.01 percent to about 4 percent by weight, and more preferably in an amount from about 0.1 percent to about 1 percent. In yet another embodiment, the composition further includes a disintegrant, preferably in an amount from about 1 percent to about 8 weight percent, more preferably from about 1 percent to about 3 weight percent.

Carriers, diluents and fillers suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, calcium carbonate, calcium phosphate, dibasic calcium phosphate, tribasic calcium sulfate, calcium carboxymethylcellulose, cellulose, cellulose (e.g., microcrystalline cellulose, silicified microcrystalline cellulose, and cellulose acetate), dextrates, dextrin, dextrose (glucose), fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, matitol, maltodextrins, maltose, sorbitol, starch (e.g., pregelatinized starch), sucrose, sugar, and xylitol.

One example of a pre-gelatinized starch is SPRESS B-820. Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa.), PROSOLV SMCC 90HD (Penwest, Patterson, N.Y.), and mixtures thereof. Carriers, diluents and fillers may also be used in premixes.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar, calcium stearate, ethyl oleate, ethyl laureate, glycerin, glyceryl palmitostearate, hydrogenated vegetable oil (e.g., corn oil, cottonseed oil, olive oil, peanut oil, sesame oil, soybean oil, and sunflower oil), magnesium oxide, magnesium stearate, mannitol, poloxamer, glycols (e.g., polyethylene glycol), sodium benzoate, sodium lauryl sulfate, sodium stearyl, sorbitol, stearic acid, talc, zinc stearate, and mixtures thereof.

Glidants include, for example, coagulated aerosols of synthetic silica colliodal silicon dioxide, magnesium trisilicate, powdered cellulose, pyrogenic silicon dioxide products (e.g., CAB-O-SIL sold by Cabot Co. of Boston, Mass.), starch, syloid silica gels (e.g., AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Md.), talc, tribasic calcium phosphate, and mixtures thereof. If used, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form the compositions of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, algins (e.g., alginic acid), calcium carbonate, carboxmethylcellulose, cellulose (e.g., hydroxypropyl cellulose, microcrystalline cellulose, and silicified microcrystalline cellulose), clays, colloid silicon dioxide, croscarmellose sodium, crospovidone, gums, magnesuim aluminium silicate, methylcellulose, polacrilin potassium, sodium alginate, sodium starch glycolate, starch (e.g., pregelatinized starch, potato starch, and tapioca starch), and mixtures thereof.

Pharmaceutical compositions and dosage forms can also contain wetting, emulsifying, and pH buffering agents.

Pharmaceutical compositions of the invention suitable for administration can be presented as discrete dosage forms, such as capsules (e.g., gelcaps), caplets, tablets, troches, lozenges, dispersions, and suppositories each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Because of their ease of administration, tablets, caplets, and capsules represent a preferred oral dosage unit forms.

Preferred tablets, caplets, and capsules contain from about 50 mg to about 500 mg of the pharmaceutical composition (i.e., active ingredient and excipient(s)), more preferably from about 125 mg to about 500 mg of the composition. Specific single unit dosage forms of the invention contain 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 750, or 1000 mg of active ingredient. Capsules can be of any size. Examples of standard sizes include #000, #00, #0, #1, #2, #3, #4, and #5. See, e.g., Remington's Pharmaceutical Sciences, page 1658-1659 (Alfonso Gennaro ed., Mack Publishing Company, Easton Pa., 18th ed., 1990). Preferred capsules of the invention are of size #0, #2, or #4.

A specific embodiment of the invention encompasses a single unit dosage form weighing about 125 mg, of which about 50 mg is active ingredient. In this embodiment, the composition is preferably loaded into a size #4 capsule. Another embodiment weighs about 250 mg, of which about 100 mg is active ingredient. In this embodiment, the composition is preferably loaded into a size #2 capsule. Yet another single unit dosage form weighs about 500 mg and contains about 200 mg active ingredient. In this embodiment, the composition is preferably loaded into a size #0 capsule.

Table 1 illustrates examples of oral dosage forms of thalidomide encompassed by the present invention:

TABLE 1

| Encapsulated thalidomide dosages | | |
|---|---|---|
| Capsule Size | Capsule Weight (mg) | Thalidomide dose (mg) |
| #0 | 500 | 200 |
| #2 | 250 | 100 |
| #4 | 125 | 50 |

Also encompassed by this invention are anhydrous pharmaceutical compositions and dosage forms including an active ingredient, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5 percent) is widely accepted in the pharmaceutical arts as a means of simulating shelf-life, i.e., long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, *Drug Stability: Principles & Practice,* 2d. Ed., Marcel Dekker, N.Y., N.Y., 1995, pp. 379-80. In effect, water and heat accelerate decomposition. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

An anhydrous pharmaceutical composition should be prepared and stored such that the anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

In this regard, the invention encompasses a method of preparing a solid pharmaceutical formulation including an active ingredient through admixing the active ingredient and an excipient under anhydrous or low moisture/humidity conditions, wherein the ingredients are substantially free of water. The method can further include packaging the anhydrous or non-hygroscopic solid formulation under low moisture conditions. By using such conditions, the risk of contact with water is reduced and the degradation of the active ingredient can be prevented or substantially reduced.

This invention further encompasses lactose-free pharmaceutical compositions and dosage forms. Compositions and dosage forms that comprise an active ingredient that is a primary or secondary amine are preferably lactose-free. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insuffficient to substantially increase the degradation rate of an active ingredient that is a primary or secondary amine.

Lactose-free compositions of the invention can comprise excipients which are well known in the art and are listed in the USP (XXI)/NF (XVI), which is incorporated herein by

reference. In general, lactose-free compositions comprise an active ingredient, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise an active ingredient, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

4.2. Process for Making Dosage Forms

Dosage forms of the present invention can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the excipient, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly admixing the active ingredient with liquid excipients or finely divided solid excipients or both, and then, if necessary, shaping the product into the desired presentation. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

A tablet or caplet of the invention can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient as above and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. Encapsulation of the dosage forms of the invention can be done using capsules of methylcellulose, calcium alginate, or gelatin.

4.2.1. Screening

The process for making the pharmaceutical compositions of the invention preferably includes the screening of the active ingredient and the excipient(s). Preferably, the active ingredient is passed through a screen having openings of about 430 microns to about 750 microns. More preferably, the active ingredient is passed through a screen with openings of about 600 microns to about 720 microns. In one embodiment, thalidomide is passed through a screen having openings of about 710 microns. Depending on the excipient (s) used, the screen openings vary. For example, disintegrants and binders are preferably passed through openings of about 430 microns to about 750 microns, more preferably from about 600 microns to about 720 microns, and most preferably about 710 microns. Lubricants are preferably passed through smaller openings, e.g., about 150 microns to about 250 microns screen. In one embodiment, the lubricant is passed through a screen opening of about 210 microns.

4.2.2. Pre-Blending

After the ingredients are screened, the excipient and active ingredient are preferably mixed in a diffusion mixer. In one embodiment, the mixing time is from about 1 minute to about 50 minutes, preferably from about 5 minutes to about 45 minutes. More preferably, the mixing time is from about 10 minutes to about 40 minutes, and most preferably the mixing time is from about 10 minutes to about 25 minutes. In another embodiment, the mixing time is about 15 minutes.

When more than one excipient is used, the excipients may be admixed in a tumble blender for about 1 minute to about 20 minutes, preferably for about 5 minutes to about 10 minutes, prior to mixing with the active ingredient.

4.2.3. Roller Compaction

In one embodiment, the pre-blend may be passed through a roller compactor with a hammer mill attached at the discharge of the compactor.

4.2.4. Final Blend

When a lubricant is used, e.g., magnesium stearate, the lubricant is mixed with the pre-blend at the end of the process to complete the pharmaceutical composition. This additional mixing is preferably from about 1 minute to about 10 minutes, more preferably about 3 minutes to about 5 minutes.

4.2.5. Encapsulation

The formulation mixture is then encapsulated into the desired size capsule shell using, for example, a capsule filling machine or a rotary tablet press.

4.3. Kits

Pharmaceutical packs or kits which comprise pharmaceutical compositions or dosage forms disclosed herein are also encompassed by the present invention. An example of a kit comprises notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

4.4. Methods of Treatment and Prevention

The present invention is also directed to methods of treating and preventing a wide variety diseases and conditions in patients (e.g., mammals, including humans). Examples of such disease and conditions include, but are not limited to, leprosy, chronic graft-vs-host disease, rheumatoid arthritis, sarcoidosis, inflammatory conditions (e.g., inflammation of the skin), inflammatory bowel disease, and cancer. Examples of cancers that can be treated using pharmaceutical compositions and dosage forms of the invention include, but are not limited to, primary and metastatic cancer of the head, neck, eye, mouth, throat, subcutaneous tissue, lymph nodes, esophagus, chest, bone, intestine, lung, colon, rectum, stomach, heart, prostate, breast, ovaries, adrenals, kidney, liver, pancreas, and brain. Specific examples of cancers that can be treated include, but are not limited to: AIDS associated leukemia and adult T-cell leukemia lymphoma; anal carcinoma; astrocytoma; biliary tract cancer; cancer of the bladder, including bladder carcinoma; brain cancer, including glioblastomas and medulloblastomas; breast cancer, including breast carcinoma; cervical cancer; choriocarcinoma; colon cancer including colorectal carcinoma; endometrial cancer; esophageal cancer; Ewing's sarcoma; gastric cancer; gestational trophoblastic carcinoma; glioma; hairy cell leukemia; head and neck carcinoma; hematological neoplasms, including acute and chronic lymphocytic and myelogeneous leukemia; hepatocellular carcinoma; Kaposi's sarcoma; kidney cancer; multiple myeloma; intraepithelial neoplasms, including Bowen's disease and Paget's disease; liver cancer; lung cancer including small cell carcinoma; lymphomas, including Hodgkin's disease, lymphocytic lymphomas, non-Hodgkin's lymphoma, Burkitt's lymphoma, diffuse large cell lymphoma, follicular mixed lymphoma, and lymphoblastic lymphoma; lympho-

cytic leukemia; neuroblastomas; oral cancer, including squamous cell carcinoma; ovarian cancer, including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells; pancreatic cancer; prostate cancer; rectal cancer; sarcomas, including soft tissue sarcomas, leiomyosarcoma, rhabdomyosarcoma, liposcarcoma, fibrosarcoma, and osteosarcoma; skin cancer, including melanoma, Kaposi's sarcoma, basal cell cancer and squamous cell cancer; testicular cancer, including testicular carcinoma and germinal tumors (e.g., semicoma, non-seminoma[teratomas, choriocarcinomas]), stromal tumors and germ cell tumors; thyroid cancer, including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinoma and Wilm's tumor. The term "colorectal carcinoma" refers to disease of skin tissues, organs, bloods, and vessels, of the colon, sigmoid, and/or rectum and within the vicinity of the colon, sigmoid, and/or rectum.

Other diseases and conditions that can be treated using pharmaceutical compositions of this invention are disclosed in U.S. Pat. Nos. 5,712,291 and 6,235,756 to D'Amato, both of which are incorporated herein by reference.

The invention also encompasses a method of reducing or preventing an adverse effect associated with chemotherapy or radiation therapy, which comprises administering to a patient in need of such treatment or prevention a pharmaceutical composition or dosage form of the invention in an amount sufficient to reduce an adverse effect associated with the chemotherapy or radiation therapy. This embodiment includes the use of pharmaceutical compositions and dosage forms to protect against or treat an adverse effect associated with the use of chemotherapy or radiation therapy, including raising a patient's tolerance for chemotherapy or radiation therapy.

Examples of adverse effects associated with chemotherapy and radiation therapy include, but are not limited to: gastrointestinal toxicity such as, but not limited to, early and late-forming diarrhea and flatulence; nausea; vomiting; anorexia; leukopenia; anemia; neutropenia; asthenia; abdominal cramping; fever; pain; loss of body weight; dehydration; alopecia; dyspnea; insomnia; dizziness, mucositis, xerostomia, and kidney failure.

The actual amount of an active ingredient administered to a patient can depend on a variety of factors, such as, but not limited to, the disease or condition being treated or prevented, the specific active ingredient, and the method of its administration. For example, the dose and/or dose frequency may also vary according to age, body weight, response, and the past medical history of the patient. Suitable dosing regimens can be readily selected by those skilled in the art with due consideration of such factors by following, for example, dosages reported in the literature and recommended in the *Physician's Desk Reference*® (55th ed., 2001).

In one embodiment of the invention, an active ingredient is administered orally and daily in an amount of from about 50 to about 2000 mg, preferably from about 50 to about 1000 mg, and more preferably from about 50 to 800 mg. In a preferred embodiment, the recommended dose of active ingredient is from about 200 mg to about 800 mg.

## 5. EXAMPLES

Embodiments of the present invention may be more fully understood by reference to the following examples. While these examples are meant to be illustrative of pharmaceutical compositions and dosage forms made according to the present invention, the present invention is not meant to be limited by the following examples. All parts are by weight unless otherwise specified.

### 5.1. Example 1

#### 200 mg Thalidomide Dosage Capsule

Table 2 illustrates a batch formulation and single dosage formulation for a 200 mg thalidomide single dose unit, i.e., about 40 percent by weight, in a size #0 capsule.

TABLE 2

Formulation for 200 mg thalidomide capsule

| Material | Percent By Weight | Quantity (mg/tablet) | Quantity (kg/batch) |
|---|---|---|---|
| Thalidomide | 40.0% | 200 mg | 16.80 kg |
| Pregelatinized Corn Starch, NF | 59.5% | 297.5 mg | 24.99 kg |
| Magnesium Stearate | 0.5% | 2.5 mg | 0.21 kg |
| Total | 100.0% | 500 mg | 42.00 kg |

The pregelatinized corn starch (SPRESS B-820) and thalidomide components were passed through a 710 μm screen and then loaded into a Diffusion Mixer with a baffle insert and blended for 15 minutes. The magnesium stearate was passed through a 210 μm screen and added to the Diffusion Mixer. The blend was then encapsulated in a size #0 capsule, 500 mg per capsule (8400 capulse batch size) using a Dosator type capsule filling machine.

### 5.2. Example 2

#### 100 mg Thalidomide Dosage Tablet

Table 3 illustrates a batch formulation and a single dose unit formulation for a 100 mg, i.e., 40 percent by weight, thalidomide single dose unit tablet.

TABLE 3

Formulation for 100 mg thalidomide tablet

| Material | Percent by Weight | Quantity (mg/tablet) | Quantity (kg/batch) |
|---|---|---|---|
| Thalidomide | 40% | 100.00 | 20.00 |
| Microcrystalline Cellulose, NF | 53.5% | 133.75 | 26.75 |
| Pluronic F-68 Surfactant | 4.0% | 10.00 | 2.00 |
| Croscarmellose Sodium Type A, NF | 2.0% | 5.00 | 1.00 |
| Magnesium Stearate, NF | 0.5% | 1.25 | 0.25 |
| Total | 100.0% | 250.00 mg | 50.00 kg |

The microcrystalline cellulose, croscarmellose sodium, and thalidomide components were passed through a #30 mesh screen (about 430μ to about 655μ). The Pluronic F-68® (manufactured by JRH Biosciences, Inc. of Lenexa, Kans.) surfactant was passed through a #20 mesh screen (about 457μ to about 1041μ). The Pluronic F-68® surfactant and 0.5 kgs of croscarmellose sodium were loaded into a 16 qt. twin shell tumble blender and mixed for about 5 minutes. The mix was then transferred to a 3 cubic foot twin shell tumble blender where the microcrystalline cellulose was added and blended for about 5 minutes. The thalidomide as added and blended for an additional 25 minutes. This

pre-blend was passed through a roller compactor with a hammer mill attached at the discharge of the roller compactor and moved back to the tumble blender. The remaining croscarmellose sodium and magnesium stearate was added to the tumble blender and blended for about 3 minutes. The final mixture was compressed on a rotary tablet press with 250 mg per tablet (200,000 tablet batch size).

### 5.3. Example 3

### Prior Art Thalidomide Dosage Unit

Table 4 illustrates a prior art batch formulation and a single dose unit formulation for a 50 mg, i.e., 12.5 percent by weight, thalidomide single dose unit sized to a capsule of size #0.

TABLE 4

| Formulation for 50 mg Thalidomide single dosage unit of size #0 | | | |
|---|---|---|---|
| Material | Percent by Weight | Quantity (mg/tablet) | Quantity (kg/batch) |
| Thalidomide | 12.5% | 50.0 | 7.50 |
| Microcrystalline Cellulose | 15.0% | 60.0 | 9.00 |
| Kollidon 90F USP[1] | 3.0% | 12.0 | 1.80 |
| Stearic Acid NF | 1.0% | 4.0 | 0.60 |
| Colloidal Silicon Dioxide | 0.2% | 0.8 | 0.12 |
| Crospovidone NF | 4.0% | 16.0 | 2.40 |
| Anhydrous lactose NF | 64.3% | 257.3 | 38.58 |
| Total | 100.0% | 400.0 mg | 60.00 kg |

[1]Also manufactured as Povidone 90F USP by BASF

Microcrystalline cellulose, KOLLIDON 90F, stearic acid, colloidal silicon dioxide, crospovidone, and anhydrous lactose were individually weighed and passed through a 710 μ screen. The raw materials were transferred into a bowl or Fielder blender. Subsequently, the quantity of milled thalidomide was weighed and added to the raw materials through the screen, followed by adding the anhydrous lactose. The mixture was blended for about 2.5 minutes to about 6 minutes, until the mixture was homogenous. The blend was compressed by passing the blend through a roller compactor (Alexanderwerk Compactor WP 50 N/75). Thereafter, the mixture was encapsulated using a Zanasi AZ20 encapsulating machine (150,000 capsule batch size). The blend mixture was loaded into size #0 hard gelatin capsules to the desired fill weight of powder and 50 mg of thalidomide.

While the invention has been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made without departing from the spirit and scope of the invention as defined in the claims. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed is:

**1**. A single unit dosage form in the form of a size 4 capsule comprising a uniform admixture of 50 mg thalidomide and 74 mg of pregelatinized corn starch.

**2**. The dosage form of claim **1**, which further comprises magnesium stearate.

**3**. The dosage form of claim **2**, wherein the magnesium stearate is present in an amount of 1 mg.

**4**. The dosage form of claim **3**, the contents of which weighs 125 mg.

**5**. A single unit dosage form in the form of a size 2 capsule, the contents of which weighs 250 mg, and comprising 100 mg of thalidomide and pregelatinized corn starch.

**6**. The dosage form of claim **5**, which further comprises magnesium stearate.

**7**. A single unit dosage form in the form of a size 0 capsule comprising a uniform admixture of 200 mg of thalidomide and 297.5 mg of pregelatinized corn starch.

**8**. The dosage form of claim **7**, which further comprises magnesium stearate.

**9**. The dosage form of claim **8**, wherein the magnesium stearate is present in an amount of 2.5 mg.

**10**. The dosage form of claim **9**, the contents of which weighs 500 mg.

* * * * *

# EXHIBIT G

US007959566B2

(12) **United States Patent**
**Williams et al.**

(10) **Patent No.: US 7,959,566 B2**
(45) **Date of Patent: *Jun. 14, 2011**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 139 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/437,551**

(22) Filed: **May 19, 2006**

(65) **Prior Publication Data**

US 2006/0224052 A1 Oct. 5, 2006

**Related U.S. Application Data**

(63) Continuation of application No. 11/028,144, filed on Jan. 3, 2005, now Pat. No. 7,141,018, which is a continuation of application No. 10/762,880, filed on Jan. 22, 2004, now Pat. No. 6,869,399, which is a continuation of application No. 10/383,275, filed on Mar. 7, 2003, now Pat. No. 6,755,784, which is a continuation of application No. 09/965,155, filed on Sep. 27, 2001, now Pat. No. 6,561,977, which is a continuation of application No. 09/694,217, filed on Oct. 23, 2000, now Pat. No. 6,315,720.

(51) **Int. Cl.**
***A61B 5/00*** (2006.01)

(52) **U.S. Cl.** ..... **600/300**; 128/920; 705/3; 235/375

(58) **Field of Classification Search** ..... 600/300–301; 128/920; 705/2–4; 235/375

See application file for complete search history.

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

**5 Claims, No Drawings**

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# METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 11/028,144, filed Jan. 3, 2005, now U.S. Pat. No. 7,141,018, which is a continuation of U.S. application Ser. No. 10/762,880, filed Jan. 22, 2004, now U.S. Pat. No. 6,869,399, which is a continuation of U.S. application Ser. No. 10/383,275, filed Mar. 7, 2003, now U.S. Pat. No. 6,755,784, which is a continuation of U.S. application Ser. No. 09/965,155, filed Sep. 27, 2001, now U.S. Pat. No. 6,561,977, which is a continuation of U.S. application Ser. No. 09/694,217, filed Oct. 23, 2000, now U.S. Pat. No. 6,315,720, the entirety of each of which is hereby incorporated by reference.

## FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

## BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

## SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the

prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;
c. in response to the information set, assigning the patient to at least one of the risk groups; and
d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

## DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing

the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk

group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the

patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional pregnancy test if a menstrual period is missed. Female

patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of childbearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via

a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed, and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuburculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment

may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative

of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

**1**. A method of treating a male patient, suffering from erythema nodosum leprosum, with thalidomide, by permitting prescriptions for thalidomide to be filled by a pharmacy only after the pharmacy has retrieved a prescription approval code for the prescription, comprising the following steps:

(a) via a non-transitory computer readable storage medium, registering a prescriber and the pharmacy with a distributor of thalidomide;

(b) determining whether the patient is able to understand and carry out instructions;

(c) upon determination that the patient is able to carry out the instructions, providing verbal and written warnings of the hazard of taking thalidomide and exposing fetus to the drug;

(d) further providing verbal and written warnings of the risk of possible contraception failure and of the need to use barrier contraception when having sexual intercourse with women of child bearing potential;

(e) obtaining acknowledgement of said warnings from the patient;

(f) providing the prescription for thalidomide to the patient from the prescriber;

(g) via a non-transitory computer readable storage medium, registering the patient with the distributor;

(h) upon obtaining the acknowledgement and registrations, generating the prescription approval code, and via a non-transitory computer readable storage medium, retrieving the prescription approval code by the pharmacy before the prescription is filled; and

(i) upon retrieving the prescription approval code, administering thalidomide to the patient.

**2**. The method of claim **1**, wherein the acknowledgement requires the patient's acknowledgement of one or more of the following:

(a) the understanding that thalidomide must not be taken if unprotected sex cannot be avoided;

(b) the understanding of potential birth defects;

(c) that the patient has been advised of the need for barrier contraception by the prescriber;

(d) the obligation to inform the prescriber if the patient's sexual partner is suspected of becoming or being pregnant;

(e) that thalidomide is solely for the use of the patient himself and must not be shared with any other person;

(f) that the patient has read the information brochure or viewed the information film on thalidomide;

(g) that the semen or blood must not be donated during the thalidomide treatment;

(h) that all of the patient's inquiries regarding thalidomide treatment have been answered by the prescribing physician; or

(i) the patient's understanding that participation in a survey and patient registry is required during the thalidomide treatment.

**3**. The method of claim **1** further comprising providing the patient, prior to generation of the approval code, with warnings of the side effects associated with administration of thalidomide, wherein said side effects are non-teratogenic side effects.

**4**. The method of claim **1** further comprising obtaining a written authorization by the prescriber prior to generation of the approval code.

**5**. The method of claim **1**, wherein the acknowledgement is a written informed consent.

* * * * *

# EXHIBIT H

US008315886B2

(12) **United States Patent**
**Williams et al.**

(10) **Patent No.: US 8,315,886 B2**
(45) **Date of Patent: *Nov. 20, 2012**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 155 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/966,261**

(22) Filed: **Dec. 13, 2010**

(65) **Prior Publication Data**

US 2011/0082707 A1 Apr. 7, 2011

**Related U.S. Application Data**

(63) Continuation of application No. 11/437,551, filed on May 19, 2006, now Pat. No. 7,959,566, which is a continuation of application No. 11/028,144, filed on Jan. 3, 2005, now Pat. No. 7,141,018, which is a continuation of application No. 10/762,880, filed on Jan. 22, 2004, now Pat. No. 6,869,399, which is a continuation of application No. 10/383,275, filed on Mar. 7, 2003, now Pat. No. 6,755,784, which is a continuation of application No. 09/965,155, filed on Sep. 27, 2001, now Pat. No. 6,561,977, which is a continuation of application No. 09/694,217, filed on Oct. 23, 2000, now Pat. No. 6,315,720.

(51) **Int. Cl.**
***G06Q 50/00*** (2006.01)

(52) **U.S. Cl.** ..... **705/2**

(58) **Field of Classification Search** ..... 705/2
See application file for complete search history.

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

**7 Claims, No Drawings**

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# METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is continuation of U.S. application Ser. No. 11/437,551, filed May 19, 2006, which is a continuation of U.S. application Ser. No. 11/028,144, filed Jan. 3, 2005, now U.S. Pat. No. 7,141,018, which is a continuation of U.S. application Ser. No. 10/762,880, filed Jan. 22, 2004, now U.S. Pat. No. 6,869,399, which is a continuation of U.S. application Ser. No. 10/383,275, filed Mar. 7, 2003, now U.S. Pat. No. 6,755,784, which is a continuation of U.S. application Ser. No. 09/965,155, filed Sep. 27, 2001, now U.S. Pat. No. 6,561,977, which is a continuation of U.S. application Ser. No. 09/694,217, filed Oct. 23, 2000, now U.S. Pat. No. 6,315,720, the entirety of each of which is incorporated herein by reference.

## FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

## BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and



aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

## SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which

prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;
c. in response to the information set, assigning the patient to at least one of the risk groups; and
d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

## DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in

detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of

child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the

patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an addi-

tional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of childbearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing

the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuberculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate

that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share

similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

**1**. A method of treating a male patient having a disease or condition responsive to a teratogenic drug comprising permitting prescriptions for the drug to be filled by a pharmacy only after the pharmacy has retrieved an approval code for the prescription, wherein the generation of the prescription approval code comprises the following steps:

(a) via a computer readable storage medium, registering a prescriber and the pharmacy with a distributor of a teratogenic drug;

(b) determining whether the patient is able to understand and carry out instructions;

(c) upon determination that the patient is able to carry out the instructions, providing verbal and written warnings of the hazard of taking the drug and exposing fetus to the drug;

(d) further providing verbal and written warnings of the risk of possible contraception failure and of the need to use barrier contraception when having sexual intercourse with women of child bearing potential;

(e) obtaining acknowledgement of said warnings from the patient;

(f) via a computer readable storage medium, registering the patient with the distributor; and

(g) upon obtaining the acknowledgement and registrations, generating via a computer readable storage medium the prescription approval code to be retrieved by the pharmacy before the prescription is filled; and

(h) upon retrieving a prescription approval code, administering the drug to the patient.

**2**. The method of claim **1**, wherein the acknowledgement requires the patient's acknowledgement of one or more of the following:

(a) the understanding that the drug must not be taken if unprotected sex cannot be avoided;

(b) the understanding of potential birth defects;

(c) that the patient has been advised of the need for barrier contraception by the prescriber;

(d) the obligation to inform the prescriber if the patient's sexual partner is suspected of becoming or being pregnant;

(e) that the drug is solely for the use of the patient himself and must not be shared with any other person;

(f) that the patient has read the information brochure or viewed the information film on the drug;

(g) that the semen or blood must not be donated during the drug treatment;

(h) that all of the patient's inquiries regarding the drug treatment have been answered by the prescribing physician; or

(i) the patient's understanding that participation in a survey and patient registry is required during the drug treatment.

**3**. The method of claim **1** further comprising providing the patient, prior to generation of the approval code, with warnings of the side effects associated with administration of the drug, wherein said side effects are non-teratogenic side effects.

**4**. The method of claim **1** further comprising obtaining a written authorization by the prescriber prior to generation of the approval code.

**5**. The method of claim **1**, wherein the prescription approval code is retrieved from a computer readable storage medium.

**6**. The method of claim **1**, wherein the acknowledgement is a written informed consent.

**7**. The method of claim **6**, wherein the written informed consent is registered in the medium prior to generation of the prescription approval code.

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# EXHIBIT I

US008626531B2

(12) **United States Patent**
**Williams et al.**

(10) **Patent No.: US 8,626,531 B2**
(45) **Date of Patent: *Jan. 7, 2014**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/591,622**

(22) Filed: **Aug. 22, 2012**

(65) **Prior Publication Data**

US 2012/0316894 A1 Dec. 13, 2012

**Related U.S. Application Data**

(63) Continuation of application No. 12/966,261, filed on Dec. 13, 2010, now Pat. No. 8,315,886, which is a continuation of application No. 11/437,551, filed on May 19, 2006, now Pat. No. 7,959,566, which is a continuation of application No. 11/028,144, filed on Jan. 3, 2005, now Pat. No. 7,141,018, which is a continuation of application No. 10/762,880, filed on Jan. 22, 2004, now Pat. No. 6,869,399, which is a continuation of application No. 10/383,275, filed on Mar. 7, 2003, now Pat. No. 6,755,784, which is a continuation of application No. 09/965,155, filed on Sep. 27, 2001, now Pat. No. 6,561,977, which is a continuation of application No. 09/694,217, filed on Oct. 23, 2000, now Pat. No. 6,315,720.

(51) **Int. Cl.**
***G06Q 50/00*** (2012.01)

(52) **U.S. Cl.**
USPC ..... **705/2**

(58) **Field of Classification Search**
USPC ..... 705/2
See application file for complete search history.

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

**40 Claims, No Drawings**

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# METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 12/966,261, filed Dec. 13, 2010, which is a continuation of U.S. application Ser. No. 11/437,551, filed May 19, 2006, now U.S. Pat. No. 7,959,566, which is a continuation of U.S. application Ser. No. 11/028,144, filed Jan. 3, 2005, now U.S. Pat. No. 7,141,018, which is a continuation of U.S. application Ser. No. 10/762,880, filed Jan. 22, 2004, now U.S. Pat No. 6,869,399, which is a continuation of U.S. application Ser. No. 10/383,275, filed Mar. 7, 2003, now U.S. Pat. No. 6,755,784, which is a continuation of U.S. application Ser. No. 09/965,155, filed Sep. 27, 2001, now U.S. Pat. No. 6,561,977, which is a continuation of U.S. application Ser. No. 09/694,217, filed Oct. 23, 2000, now U.S. Pat. No. 6,315,720, the entirety of each of which is incorporated herein by reference.

## FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

## BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

## SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while

avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;
c. in response to the information set, assigning the patient to at least one of the risk groups; and
d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

## DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the

methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug,

such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the pre-

scriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree

to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of childbearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuburculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is

not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol.

Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

**1**. A system for communicating over a network with a pharmacist for authorizing delivery of a contraindicated drug to a patient, the patient pre-assigned to at least one risk group of a plurality of risk groups, the plurality of risk groups defined based on factors which indicate one or more risks of one or more adverse side effects if the patient receives the drug, the system comprising:

a computer device including:

a computer readable medium having stored therein the plurality of risk groups, the at least one risk group assignment, and registration information of the patient;

the computer device configured to provide:

an interface configured to receive an on-line transmission of a pharmacist prescription for the patient in order to dispense the contraindicated drug to the patient;

a generator configured to generate a prescription approval code based on comparison of the on-line transmission of the pharmacist prescription for the patient with the registration information of the patient stored in the computer readable medium to confirm if the patient is registered, and based on comparison of the on-line transmission of the pharmacist prescription for the patient with the risk group assignment stored in the computer readable medium to determine if the patient is eligible to receive the contraindicated drug, such that the risk group assignment is based on a predefined set of risk parameters for the contraindicated drug; and

an interface configured to send an on-line transmission to the pharmacist including the generated prescription approval code when the registered patient is eligible to receive the drug;

wherein the pharmacist can proceed with dispensation of the drug to the patient on the basis of the generated prescription approval code once received.

**2**. The system of claim **1** further comprising the computer readable medium having stored thereon further information selected from the group comprising: registration of the pharmacist as qualified to fill a prescription for the drug and registration of a prescriber as qualified to prescribe the drug.

**3**. The system of claim **2**, wherein the further information includes an informed consent of the patient for receiving the drug.

**4**. The system of claim **3**, wherein the further information is compared with the drug request before generation of the prescription approval code.

**5**. The system of claim **4**, wherein the patient registration information includes information selected from the group comprising: name; age; sex; mailing address; date of birth; specified prescriber for the drug; history of drug prescription; medical condition; medical patient history; and lifestyle.

**6**. The system of claim **4**, wherein the drug is a teratogen intended for prescription for activity selected from the group comprising: disease diagnosis; disease cure; disease mitigation; disease treatment or prevention; and to affect the structure or function of the body of the patient.

7. The system of claim 4, wherein the one or more adverse side effects of the drug is selected from the group comprising: abnormality; defect; mutation; lesion; degeneration; and injury.

8. The system of claim 7, wherein an individual having the one or more risks of the one or more adverse side effects is selected from the group comprising: the patient, a foetus of the patient, and a foetus carried by a recipient of bodily fluid of the patient.

9. The system of claim 8, wherein the drug is one of a plurality of drugs available to the patient and the one or more risks of the one or more adverse side effects is defined in the risk group assignment as from a combination of the plurality of drugs.

10. The system of claim 1 further comprising additional communication over the network via on-line communication.

11. The system of claim 10 further comprising the interface including an integrated voice response system such that the network is a telecommunications network.

12. The system of claim 1 computer readable medium having stored thereon risk parameters assigned to the plurality of risk groups, such that the at least one risk group includes a risk parameter selected from the group comprising: female patients of child bearing potential; female patients of non-child bearing potential; sexually active male patients; sexually inactive male patients; patients to whom administration of the drug may be strictly contraindicated; factors influencing a likelihood that certain pre-existing conditions may exist; and factors indicating a likelihood of certain other drugs being used concomitantly with the drug.

13. The system of claim 12 further comprising the on-line transmission to the pharmacist such that the generated prescription approval code is omitted from the on-line transmission to the pharmacist and a request for additional information is included in the on-line transmission to the pharmacist, the additional information selected from the group comprising: a survey for a set of information to be collected from the patient that is probative of the one or more risks of the one or more adverse side effects to occur if the drug is provided to the patient; and a diagnostic test result associated with the patient.

14. The system of claim 13, wherein the diagnostic test result is selected from the group comprising: genetic test results; pregnancy test results; and evidence of use of another drug different from the drug of the on-line transmission of the pharmacist prescription.

15. The system of claim 13 further configured such that the least one risk group assigned to the patient defines the additional information for the request for additional information included in the on-line transmission to the pharmacist.

16. The system of claim 15, wherein the additional information is defined for updating parameters of the patient risk group assignment on a periodic basis.

17. The system of claim 16, wherein the providing of the additional information to the computer readable medium results in an update of the patient risk group assignment.

18. The system of claim 15 further comprising the interface configured for providing the generated approval code once the registered patient is deemed eligible to receive the drug in view of the update to the patient risk group assignment.

19. The system of claim 12, wherein the on-line transmission of the pharmacist prescription is selected from the group comprising: an initial prescription for the drug and a prescription refill for the drug.

20. The system of claim 19, wherein additional information when received by the interface in reply to the request for additional information is stored in the computer readable medium.

21. A method for communicating over a network with a pharmacist for authorizing delivery of a contraindicated drug to a patient, the patient pre-assigned to at least one risk group of a plurality of risk groups, the plurality of risk groups defined based on factors which indicate one or more risks of one or more adverse side effects if the patient receives the drug, the method comprising the steps of:

accessing, using a computer device, a computer readable medium having stored thereon the plurality of risk groups, the at least one risk group assignment, and registration information for the patient in computer readable medium;

receiving, using the computer device, an on-line transmission of a pharmacist prescription for the patient in order to dispense the contraindicated drug to the patient;

comparing, using the computer device, the on-line transmission of the pharmacist prescription for the patient with the registration information of the patient stored in the computer readable medium to confirm if the patient is registered, and comparing of the on-line transmission of the pharmacist prescription for the patient with the risk group assignment stored in the computer readable medium to determine if the patient is eligible to receive the contraindicated drug,

generating, using the computer device, a prescription approval code based on comparison of the on-line transmission of the pharmacist prescription for the patient if confirmed the registered patient is eligible to receive the drug; and

sending, sing the computer device, an on-line transmission to the pharmacist including the generated prescription approval code when the registered patient is eligible to receive the drug;

wherein the pharmacist can proceed with dispensation of the drug to the patient on the basis of the generated prescription approval code once received.

22. The method of claim 21 further comprising the step of storing further information selected from the group comprising: registration of the pharmacist as qualified to fill a prescription for the drug and registration of a prescriber as qualified to prescribe the drug.

23. The method of claim 22, wherein the further information includes an informed consent of the patient for receiving the drug.

24. The method of claim 23, wherein the further information is compared with the drug request before generation of the prescription approval code.

25. The method of claim 24, wherein the patient registration information includes information selected from the group comprising: name; age; sex; mailing address; date of birth; specified prescriber for the drug; history of drug prescription; medical condition; medical patient history; and lifestyle.

26. The method of claim 24, wherein the drug is a teratogen intended for prescription for activity selected from the group comprising: disease diagnosis; disease cure; disease mitigation; disease treatment or prevention; and to affect the structure or function of the body of the patient.

27. The method of claim 24, wherein the one or more adverse side effects of the drug is selected from the group comprising: abnormality; defect; mutation; lesion; degeneration; and injury.

**28**. The method of claim **27**, wherein an individual having the one or more risks of the one or more adverse side effects is selected from the group comprising: the patient, a foetus of the patient, and a foetus carried by a recipient of bodily fluid of the patient.

**29**. The method of claim **28**, wherein the drug is one of a plurality of drugs available to the patient and the one or more risks of the one or more adverse side effects is defined in the risk group assignment as from a combination of the plurality of drugs.

**30**. The method of claim **21** further comprising additional communication over the network via on-line communication.

**31**. The method of claim **30**, wherein the receiving of the on-line transmission of the pharmacist prescription is via an integrated voice response system such that the network is a telecommunications network.

**32**. The method of claim **21** further comprising the step of storing risk parameters assigned to the plurality of risk groups, such that the at least one risk group includes a risk parameter selected from the group comprising: female patients of child bearing potential; female patients of non-child bearing potential; sexually active male patients; sexually inactive male patients; patients to whom administration of the drug may be strictly contraindicated; factors influencing a likelihood that certain pre-existing conditions may exist; and factors indicating a likelihood of certain other drugs being used concomitantly with the drug.

**33**. The method of claim **32** further comprising the step of omitting the generated prescription approval code from the on-line transmission to the pharmacist and including a request for additional information in the on-line transmission to the pharmacist, the additional information selected from the group comprising: a survey for a set of information to be collected from the patient that is probative of the one or more risks of the one or more adverse side effects to occur if the drug is provided to the patient; and a diagnostic test result associated with the patient.

**34**. The method of claim **33**, wherein the diagnostic test result is selected from the group comprising: genetic test results; pregnancy test results; and evidence of use of another drug different from the drug of the on-line transmission of the pharmacist prescription.

**35**. The method of claim **33**, wherein the least one risk group assigned to the patient defines the additional information for the request for additional information included in the on-line transmission to the pharmacist.

**36**. The method of claim **35** further comprising the step of using the additional information obtained from the patient for updating parameters of the patient risk group assignment on a periodic basis.

**37**. The method of claim **36** further comprising the step of using the additional information to update the patient risk group assignment.

**38**. The method of claim **35** further comprising the step of providing the generated prescription approval code once the registered patient is deemed eligible to receive the drug in view of the update to the patient risk group assignment.

**39**. The method of claim **32**, wherein the on-line transmission of the pharmacist prescription is selected from the group comprising: an initial prescription for the drug and a prescription refill for the drug.

**40**. The method of claim **39** further comprising the step of storing the additional information in the computer readable medium when received in reply to the request for additional information.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION



PATENT NO. : 8,626,531 B2
APPLICATION NO. : 13/591622
DATED : January 7, 2014
INVENTOR(S) : Bruce A. Williams and Joseph K. Kaminski

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 19,
Claim 15, lines 49-50, delete "that the least" and insert -- that the at least --.

Column 20,
Claim 21, line 35, delete "sing the computer device," and insert -- using the computer device, --.

Column 22,
Claim 35, line 10, after "wherein the" insert -- at --.

Signed and Sealed this
First Day of April, 2014

Michelle K. Lee

Michelle K. Lee
*Deputy Director of the United States Patent and Trademark Office*

UNITED STATES PATENT AND TRADEMARK OFFICE

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 20,
Claim 20, line 1, delete "claim 19," and insert -- claim 13, --.

Column 22,
Claim 40, line 29, delete "claim 39" and insert -- claim 33 --.

Signed and Sealed this
Fourteenth Day of June, 2016

Michelle K. Lee

Michelle K. Lee
*Director of the United States Patent and Trademark Office*